

**THE EFFECT OF ADRENOCORTICOTROPIC HORMONE ON  
CHILDREN WITH THE NEPHROTIC SYNDROME. II.  
PHYSIOLOGIC OBSERVATIONS ON DISCRETE KIDNEY  
FUNCTIONS AND PLASMA VOLUME**

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PHYSIOLOGIC OBSERVATIONS ON DISCRETE  
KIDNEY FUNCTIONS AND PLASMA  
VOLUME<sup>1</sup>

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INTRODUCTION

Inability to predict the time of occurrence of spontaneous diureses in the nephrotic syndrome has retarded investigations of the physiologic changes which may precede, accompany, and follow these heartening but enigmatic events. It has been demonstrated recently that several agents (1-5) are capable of *inducing* diureses at a predictable time in a far higher percentage of trials than could be attributed to chance. Adrenocorticotrophic hormone (ACTH) is one such agent, and the abrupt, profuse, and sustained diureses which may accompany or follow its administration are clinically similar to the dramatic diureses which occur spontaneously. Clinical observations on the effect of ACTH<sup>4</sup> on a group of children with the nephrotic syndrome is the subject of a separate report (6) in which the possible clinical significance of the results is also discussed. Serial physiologic measurements were made on selected patients before, during, and after administration of ACTH. These observations were directed toward an increased understanding of the syndrome itself and especially of the mechanism of diuresis rather than

toward evaluation of possible relationships between the disease and pituitary or adrenocortical function. As an integral part of the approach, an attempt was made to disclose, if possible, consistent changes which might precede the outset of diuresis and, to this end, as many relevant physiologic measurements as practicable were made. These included: blood volume; discrete kidney functions; concentrations of electrolytes and nitrogenous constituents of serum; metabolic balances of electrolytes and nitrogen; serum lipid fractions; and urinary protein and sediment.

It has not been possible from any one or combination of changes to predict when diuresis would occur in relation to administration of ACTH. The most striking changes observed after the outset of diuresis were increases in plasma volume and unexpectedly large increases in glomerular filtration rate (GFR). These changes together with observations on other discrete kidney functions are described in the present paper. Observations on other measurements will be the subject of a subsequent report (7).

SUBJECTS AND METHODS

Observations were made on eight children with the nephrotic syndrome whose clinical status and course during ACTH administration is described in a separate report (6). Clinical data relevant to the observations presented here are included in Table I.

Various combinations of the following measurements

<sup>1</sup> Presented in part before the Society of Pediatric Research at French Lick, Indiana, on May 9, 1950.

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<sup>4</sup> We wish to thank Dr. John R. Mote of the Armour Laboratories for allocating the ACTH used in these observations.

were made before, during, and after administration of ACTH: daily weight; plasma volume and hematocrit; clearances of inulin ( $C_{IN}$ ); endogenous creatinine ( $C_{CR}$ ); thiosulfate ( $C_{THIO}$ ) and p-aminohippurate ( $C_{PAH}$ ); and maximum tubular excretion of PAH ( $T_{M_{PAH}}$ ). In three children (I. C., K. N., J. S.), 24-hour clearances of endogenous creatinine ( $C_{CR-24}$ ) were measured. These children were on low salt (20 meq. per day) but otherwise normal diets. Most of the time they were ambulatory and normally active.

Methods for inulin, p-aminohippurate, urea (8) and endogenous creatinine (9), in blood and urine, and the catheterization and infusion technic used for short-term simultaneous clearances have been described (8). Serum and urine thiosulfate concentrations were determined by the method of Newman, Gilman, and Phillips (10).  $C_{CR-24}$  was calculated using 24-hour creatinine excretion and mid-point serum values interpolated from creatinine determinations made one to three days apart. Plasma volume was measured with T-1824 using a single 10-minute blood sample and the acetone extraction method of Chinard and Eder (11) for lipemic sera. Blood volume was calculated from plasma volume and hematocrit (12).

#### RESULTS<sup>5</sup>

Changes observed in discrete kidney functions and plasma volume in relation to hormone administration are given in Table I. Data from B. B. and I. C. are shown graphically in Figures 1 and 2.

##### Glomerular filtration rate

The most striking changes observed during or following diureses associated with ACTH administration were marked increases in  $C_{IN}$ . Such increases were observed on eight occasions in six of the eight children and were greatest in patients with low initial values. Thus increases in  $C_{IN}$  of 179, 211, 190, 50, and 256% above control values were observed respectively in I. C., K. N., B. B., M. L., and S. S.<sup>6</sup> In B. B., this change in  $C_{IN}$  represents an increase from 35 to 133% of normal (Figure 1). In the three children whose initial values were within the normal range, measure-

<sup>5</sup> The frequency with which diuresis has been observed with ACTH in children with the nephrotic syndrome is reported separately (6). In this group of eight children, selected because measurements had been made both before and after ACTH, a diuresis failed to occur in only one of 14 courses. This failure occurred when only 50 mg. per day for three and one half days was given to a child (I. C.) who diuresed on three other occasions with larger dosages.

<sup>6</sup> Only a small fraction of the observed increases in  $C_{IN}$  could be related to increases in rate of urine flow during diuresis.

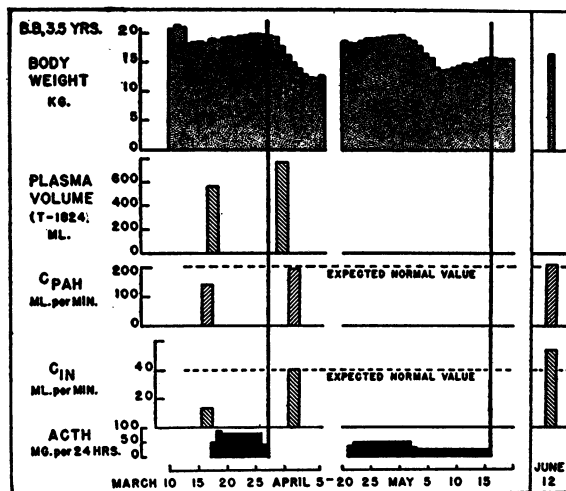


FIG. 1. RELATION OF CHANGES IN BODY WEIGHT, PLASMA VOLUME, AND CLEARANCES OF INULIN AND P-AMINOHIPPUATE TO ADMINISTRATION OF ACTH IN A CHILD WITH THE NEPHROTIC SYNDROME

ments of  $C_{IN}$  showed no significant increase in two (J. S. and R. T.), but revealed an increase to the high value of 123% of normal in one (R. K.). Failure to observe an increase in  $C_{IN}$  following diuresis (as in I. C., February 1) may possibly be due to failure to make the measurement at the proper time as discussed later.

In an attempt to determine when changes in GFR occurred and to follow their course, 24-hour clearances of endogenous creatinine were measured. The ratio of  $C_{CR} : C_{IN}$  is irregularly greater than one in children with kidney disease (17). Consequently, repeated short term measurements of this ratio were made to relate changes in the 24-hour clearance to changes in GFR. Even though changes in this ratio were taken into account,  $C_{CR-24}$  was interpreted only as reflecting changes in rather than as an absolute measure of GFR. Despite these reservations, changes in  $C_{CR-24}$  were sufficiently large to demonstrate that GFR increased during the first 24 hours of diuresis, as shown in Figure 2. Additional impressions concerning changes in GFR during and following ACTH administration are gained from inspection of the data from I. C.<sup>7</sup>

<sup>7</sup> In this patient and in others receiving cortisone in larger dosages no diuresis occurred and no increase in GFR was observed. On the contrary, a marked fall in GFR was observed in S. S. 15 days after he had received 100 mg. of cortisone in seven days. There are not sufficient data to indicate the significance of this observation.

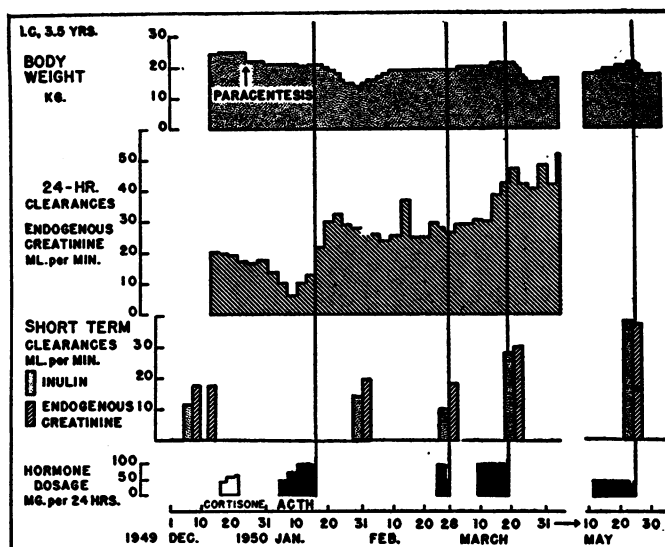


FIG. 2. RELATION OF CHANGES IN BODY WEIGHT AND CLEARANCES OF INULIN AND ENDOGENOUS CREATININE TO ADMINISTRATION OF ACTH IN A CHILD WITH THE NEPHROTIC SYNDROME

The decrease in  $C_{CR-24}$  seen during the first course of ACTH administration (January 4 to 16) has been observed in other patients and was often associated with a marked rise in serum urea nitrogen and endogenous creatinine. These changes suggest a temporary fall in GFR during ACTH administration. The low value for  $C_{IN}$  measured on February 28, one day after a three day course of ACTH which did not induce diuresis, lends support to this impression.<sup>8</sup> The pattern of changes in  $C_{CR-24}$  in Figure 2 suggests that each diuresis was accompanied by an increase in GFR and followed by a decrease from the maximum value with subsequent stabilization at a value slightly or markedly above the control. It is possible that the fall in GFR may already have occurred when  $C_{IN}$  was measured on February 1, 1950, since re-accumulation of edema already had begun. Repeated responses to ACTH may, however, be as-

<sup>8</sup>  $C_{CR}$ , measured simultaneously with  $C_{IN}$ , showed a comparable decrease at this time. Failure of  $C_{CR-24}$  to reflect this decrease may be partly explained by the inaccuracy of calculating clearances using mid-point values for serum creatinine concentrations interpolated from determinations made on fasting samples taken at intervals of several days (18).  $C_{CR-24}$  was consistently higher than  $C_{CR}$  which might be expected from the fact that the latter was always measured early in the day with the subject at rest and in a fasting state, whereas the former might be affected by such factors as eating and activity.

sociated, as shown in Figures 1 and 2, with a progressive increase in GFR to normal (I. C.) or even "supernormal" values (B. B.).

Changes of this order of magnitude in  $C_{IN}$  in children with diseased kidneys must raise the question of the validity of  $C_{IN}$  as a measure of GFR under these conditions. This question becomes especially pertinent in view of the consistent changes observed in three children (I. C., K. N., and B. B.) in the  $C_{CR} : C_{IN}$  ratio which decreased from a range of 1.5 to 1.9 before to a range of 1.0 to 1.4 after diuresis. However, the reasonably good agreement between  $C_{IN}$  and  $C_{THIO}$  ( $C_{THIO} : C_{IN}$  ratios ranging from 0.9 to 1.2) at both decreased and increased values of  $C_{IN}$  provides evidence that  $C_{IN}$  was a measure of GFR in these children. The changes observed in the  $C_{CR} : C_{IN}$  ratio are unexplained at present.

#### *Effective renal plasma flow ( $C_{PAH}$ )*

Significant and consistent increases in  $C_{PAH}$  were observed to accompany increases in  $C_{IN}$  during diureses occurring with ACTH. However, increases in  $C_{PAH}$  were consistently less than those in  $C_{IN}$  so that in the six children (I. C., K. N., B. B., R. K., M. L., and S. S.) who showed an increase in  $C_{IN}$  the  $C_{IN} : C_{PAH}$  ratio increased from a range of 0.10 to 0.17 before to a range of 0.22 to 0.32 after diuresis. Whether these changes

TABLE 1—Measurements of discrete kidney functions\* and plasma volume in relation to hormone administration

The New York Hospital																	
Subject	Date	Hormone administration	Weight kg.	C <sub>IN</sub> ml. per min.	CCR ml. per min.	C <sub>THIO</sub> ml. per min.	C <sub>PAH</sub> ml. per min.	T <sub>MPAH</sub> mg. per min.	C <sub>IN</sub> / C <sub>PAH</sub>	CCR/ C <sub>IN</sub>	C <sub>THIO</sub> / C <sub>IN</sub>	C <sub>IN</sub> / T <sub>MPAH</sub>	Plasma volume ml.	Blood volume ml.	Hemato- crit %	Comment	
I. C. F. Age 3.5 yrs. Ht. 96.0 cm. Wt. 15.2 kg.† S.A. 0.62M‡	12/7/49	Cortisone 335 mg. (6d)	23.4	11.9	18.0	12.0	77.9	—	0.15	1.5	1.0	—	—	—	—	Duration of disease—7 mos. Constant edema since outset with no spontaneous diuresis.	
	12/12		24.4	—	—	—	—	—	—	—	—	—	—	—	—		
	12/16-21		24.7-25.2	—	—	—	—	—	—	—	—	—	—	—	—		
	1/4/50	ACTH 1000 mg. (13d)†	21.4	—	—	—	—	—	—	—	—	—	—	—	—	Diuresis 15th day after start of therapy (1/19). Minimum weight following diuresis. Outset of reaccumulation of edema. Maximum weight. No diuresis.	
	1/4-16		21.4-20.9	—	—	—	—	—	—	—	—	—	—	—	—		
	1/19		20.3	—	—	—	—	—	—	—	—	—	—	—	—		
	1/30	14.2	14.3	19.9	12.8	—	—	—	—	—	—	—	—	—			
	2/1	14.6	—	—	—	—	—	—	—	—	—	—	—	—			
	2/16	19.1	—	—	—	—	—	—	—	—	—	—	—	—	—		
	2/23	ACTH 350 mg. (34d)	18.5-19.1	—	—	—	—	—	—	—	—	—	—	—	—	Diuresis 13th day after start of therapy (3/21). Minimum weight following diuresis. Outset of reaccumulation of edema.	
	2/24-27		19.3	10.1	18.6	70.9	—	0.14	1.8	—	—	—	663	1074	40.0		
	2/28		19.6	—	—	—	—	—	—	—	—	—	—	—	—		
3/7	ACTH 950 mg. (94d)	19.6-21.4	28.2	30.4	—	119	—	0.24	1.1	—	—	853	1218	31.4	Diuresis 15th day after start of therapy (5/26). In apparent clinical remission 12/1/50.		
3/21		20.9	—	—	—	—	—	—	—	—	—	—	—	—			
3/22		20.0	—	—	—	—	—	—	—	—	—	—	—	—			
3/27	ACTH 687.5 mg. (14d)	15.0	—	—	—	—	—	—	—	—	—	—	—	—	Duration of disease—10 mos. Constant edema since outset with no spontaneous diuresis. Diuresis 9th day after start of therapy (1/29). Minimum weight following diuresis. Outset of reaccumulation of edema. Maximum weight.		
3/30		15.4	—	—	—	—	—	—	—	—	—	—	—	—			
5/10		17.5	—	—	—	—	—	—	—	—	—	—	—	—			
5/11-24	ACTH 687.5 mg. (14d)	17.2-20.7	38.2	37.5	33.2	106	—	0.36	1.0	—	—	—	—	—	Diuresis 15th day after start of therapy (5/26). In apparent clinical remission 12/1/50.		
5/24		20.7	—	—	—	—	—	—	—	—	—	—	—	—			
5/26		20.1	—	—	—	—	—	—	—	—	—	—	—	—			
11/16	Expected normal value §	—	—	—	—	—	—	—	0.20	—	—	—	—	—	—		
K. N. M. Age 3 yrs. Ht. 91.5 cm. Wt. 14.1 kg. S.A. 0.58M‡	1/20/50	ACTH 675 mg. (8d)	20.5	8.1	16.6	—	71.9	—	0.11	2.0	—	—	—	—	—	Duration of disease—10 mos. Constant edema since outset with no spontaneous diuresis. Diuresis 9th day after start of therapy (1/29). Minimum weight following diuresis. Outset of reaccumulation of edema. Maximum weight.	
	1/20-27		20.5-20.6	—	—	—	—	—	—	—	—	—	—	—	—		—
	1/29		20.3	—	—	—	—	—	—	—	—	—	—	—	—		—
	2/3	ACTH 950 mg. (94d)	14.3	25.2	30.1	—	94.2	—	0.27	1.2	—	—	553	819	34.0	Diuresis 6th day after start of therapy (3/10). Minimum weight following diuresis. Outset of reaccumulation.	
	2/6		12.2	—	—	—	—	—	—	—	—	—	—	—	—		
	2/9		12.5	—	—	—	—	—	—	—	—	—	—	—	—		
	3/3	ACTH 950 mg. (94d)	18.4	—	—	—	—	—	—	—	—	—	—	—	—	Diuresis 6th day after start of therapy (3/10). Minimum weight following diuresis. Outset of reaccumulation.	
	3/4-13		18.3-17.4	—	—	—	—	—	—	—	—	—	—	—	—		
	3/10		19.7	—	—	—	—	—	—	—	—	—	—	—	—		
	3/11	ACTH 537.5 mg. (11d)	19.1	—	—	—	—	—	—	—	—	—	645	904	30.0	Minimum weight following diuresis. Outset of reaccumulation. Maximum weight. Diuresis 8th day after start of therapy (4/29). Minimum weight following diuresis. In apparent clinical remission 12/1/50. No manifest edema.	
	3/13		17.4	—	—	—	—	—	—	—	—	—	—	—	—		
	3/18		12.4	—	—	—	—	—	—	—	—	—	—	—	—		
	3/21	ACTH 537.5 mg. (11d)	12.9	—	—	—	—	—	—	—	—	—	—	—	—	Minimum weight following diuresis. Outset of reaccumulation. Maximum weight. Diuresis 8th day after start of therapy (4/29). Minimum weight following diuresis. In apparent clinical remission 12/1/50. No manifest edema.	
	4/20		15.9	—	—	—	—	—	—	—	—	—	—	—	—		
	4/21		16.2	—	—	—	—	—	—	—	—	—	—	—	—		
	4/21-5/1	ACTH 537.5 mg. (11d)	16.2-15.4	—	—	—	—	—	—	—	—	—	—	—	—	Minimum weight following diuresis. Outset of reaccumulation. Maximum weight. Diuresis 8th day after start of therapy (4/29). Minimum weight following diuresis. In apparent clinical remission 12/1/50. No manifest edema.	
	4/29		17.2	—	—	—	—	—	—	—	—	—	—	—	—		
4/30	16.6		—	—	—	—	—	—	—	—	—	—	—	—			
4/31	ACTH 537.5 mg. (11d)	16.1	—	—	—	—	—	—	—	—	—	—	—	—	Minimum weight following diuresis. In apparent clinical remission 12/1/50. No manifest edema.		
5/4		13.9	—	—	—	—	—	—	—	—	—	—	—	—			
5/31		16.1	—	—	—	—	—	—	—	—	—	—	—	—			
11/17	Expected normal value	—	—	—	—	—	—	—	0.35	1.4	—	—	—	—	—		
—	—	—	—	—	—	—	—	—	0.20	—	—	—	—	—	—		

\* Each value represents the average of three or more 10 to 20 minute clearance periods.

† Daily dosage of ACTH was given in four divided doses at six hour intervals.

‡ Ideal weight for height and age (13) was used for the estimation of surface area (14) from which expected normal values for renal plasma clearances were calculated.

§ These values were calculated as follows:

$$\text{Expected normal value} = \frac{\text{Surface area of child (M}^2\text{)}}{1.73\text{M}^2} \times \text{normal adult value corrected to } 1.73\text{M}^2.$$

Since there is no evidence that a sex difference in renal functions exists in children before puberty, a single normal adult value for each discrete function was used to calculate expected normal values for both boys and girls. These values were arbitrarily taken as the average of mean values for normal men and women (15). Per unit of surface area, values for discrete kidney functions for children of this age are expected to be within the normal adult range (16).

|| Day on which weight loss of 0.2 kg. or greater was first observed and which was followed by continued loss of body weight.

TABLE 1—Continued

Subject	Date	Hormone administration	Weight kg.	C <sub>IN</sub> ml. per min.	CCR ml. per min.	C <sub>THIO</sub> ml. per min.	C <sub>PAH</sub> ml. per min.	T <sub>MPAH</sub> mg. per min.	C <sub>IN</sub> / C <sub>PAH</sub>	CCR/ C <sub>IN</sub>	C <sub>THIO</sub> / C <sub>IN</sub>	C <sub>IN</sub> / T <sub>MPAH</sub>	Plasma volume ml.	Blood volume ml.	Hemato- crit %	Comment
B. B. F.1 Age 3.5 yrs. Ht. 90.0 cm. Wt. 13.7 kg. S.A. 0.57M <sup>3</sup>	3/16/50	ACTH 740 mg. (9d)	18.3	14.0	28.1	16.2	148	—	0.09	2.0	1.2	—	615	—	25.6	Duration of disease—7 mos. Constant edema since onset with no spontaneous diuresis. Diuresis 11th day after start of therapy (3/28). Minimum weight following diuresis. Maximum weight. Diuresis 10th day after start of therapy (5/1). Minimum weight following therapy. In apparent clinical remission 5/9–10/1. Reaccumulation of edema 10/1/50. 13 days ACTH therapy (525 mg.) resulted in diuresis.
	3/17		19.0	—	—	—	—	—	—	—	—	—	—	814	—	
	3/17–26		19.0–19.8	—	—	—	—	—	—	—	—	—	—	—	—	
	3/28		19.3	—	—	—	—	—	—	—	—	—	—	—	—	
	3/29		17.7	—	—	—	—	—	—	—	—	—	—	—	—	
	3/31		14.8	40.6	44.5	39.0	197	—	0.21	1.1	1.0	—	774	—	—	
	4/3		12.4	—	—	—	—	—	—	—	—	—	—	—	—	
	4/20		18.6	—	—	—	—	—	—	—	—	—	—	—	—	
	4/21		18.4	—	—	—	—	—	—	—	—	—	—	—	—	
	4/21–5/15		18.4–15.9	—	—	—	—	—	—	—	—	—	—	—	—	
	5/1		19.1	—	—	—	—	—	—	—	—	—	—	—	—	
	5/7		13.6	—	—	—	—	—	—	—	—	—	—	—	—	
	5/9		14.1	—	—	—	—	—	—	—	—	—	—	—	—	
J. S. M. Age 3.2 yrs. Ht. 95.0 cm. Wt. 15.0 kg. S.A. 0.61M <sup>3</sup>	3/6/50	ACTH 625 mg. (61d)	13.9	41.2	57.9	46.3	196	—	0.21	1.4	1.1	—	678	1064	38.0	Duration of disease—2.5 mos. One spontaneous diuresis 4 weeks after outset. Minimal edema at start of therapy. Diuresis 8th day after start of therapy (4/22). Minimum weight following diuresis. Moderate intermittent peripheral edema 12/1/50.
	4/11		15.3	45.8	58.6	—	196	—	0.23	1.3	—	—	—	—	—	
	4/12		—	—	—	—	—	—	—	—	—	—	—	—	—	
	4/14–20		15.6–15.9	—	—	—	—	—	—	—	—	—	—	—	—	
	4/21		15.7	—	—	—	—	—	—	—	—	—	—	—	—	
	4/22		15.2	42.8	46.4	—	193	—	0.22	1.1	—	—	750	1143	36.0	
	4/24		14.7	—	—	—	—	—	—	—	—	—	—	—	—	
	8/31		18.0	45.5	—	—	221	—	0.20	—	—	—	—	—	—	
	Expected normal value		—	—	—	—	—	—	—	—	—	—	—	—	—	
	7/10/50	ACTH 500 mg. (11d)	27.4	37.1	48.1	—	212	—	0.18	1.3	—	—	933	1510	40.0	
	7/11		27.8	—	—	—	—	—	—	—	—	—	—	—	—	
	7/12		27.6	—	—	—	—	—	—	—	—	—	—	—	—	
	7/12–22		27.6–27.8	—	—	—	—	—	—	—	—	—	—	—	—	
	7/23		27.2	—	—	—	—	—	—	—	—	—	—	—	—	
	7/27		19.3	56.0	64.5	—	233	—	0.24	1.2	—	—	918	1463	39.0	
	8/1		17.2	—	—	—	—	—	—	—	—	—	—	—	—	
	8/11		21.8	—	—	—	—	—	—	—	—	—	—	—	—	
	11/26		—	45.5	—	—	233	—	0.20	—	—	—	—	—	—	
	Expected normal value		—	—	—	—	—	—	—	—	—	—	—	—	—	
	7/10/50	ACTH 500 mg. (11d)	27.4	37.1	48.1	—	212	—	0.18	1.3	—	—	933	1510	40.0	Duration of disease—11 mos. One diuresis in March 1950 following paracentesis. Reaccumulation of edema 4 months later. Diuresis 11th day after start of therapy (7/23). Minimum weight following diuresis. Reaccumulation of edema and spontaneous diuresis in October and again in November.
	7/11		27.8	—	—	—	—	—	—	—	—	—	—	—	—	
	7/12		27.6	—	—	—	—	—	—	—	—	—	—	—	—	
	7/12–22		27.6–27.8	—	—	—	—	—	—	—	—	—	—	—	—	
	7/23		27.2	—	—	—	—	—	—	—	—	—	—	—	—	
	7/27		19.3	56.0	64.5	—	233	—	0.24	1.2	—	—	918	1463	39.0	
	8/1		17.2	—	—	—	—	—	—	—	—	—	—	—	—	
	8/11		21.8	—	—	—	—	—	—	—	—	—	—	—	—	
	11/26		—	45.5	—	—	233	—	0.20	—	—	—	—	—	—	
	Expected normal value		—	—	—	—	—	—	—	—	—	—	—	—	—	

TABLE I—Continued

Children's Hospital of Philadelphia

Subject	Date	Hormone administration	Weight kg.	C <sub>IN</sub> ml. per min.	CCR ml. per min.	C <sub>THIO</sub> ml. per min.	C <sub>PAH</sub> ml. per min.	T <sub>MPAH</sub> mg. per min.	C <sub>IN</sub> / C <sub>PAH</sub>	CCR/ C <sub>IN</sub>	C <sub>THIO</sub> / C <sub>IN</sub>	C <sub>IN</sub> / T <sub>MPAH</sub>	Plasma volume ml.	Blood volume ml.	Hemato- crit %	Comment
R. T. M. Age 3 yrs. Ht. 91.5 cm. Wt. 14.5 kg. S.A. 0.58M <sup>2</sup>	1/4/50	Cortisone 1300 mg. (17d)	17.5	49.4	—	—	160	31.3	0.31	—	—	1.6	—	—	—	Duration of disease—4 mos. Constant edema since onset with no spontaneous diuresis. No diuresis following Cortisone. No diuresis.
	1/6-22		—	—	—	—	—	—	—	—	—	—	—	—	—	
	1/16		20.0	45.1	—	—	220	39.0	0.21	—	—	1.2	—	—	—	
	2/20	Cortisone 575 mg. (8d) DCA 40 mg.	16.8	37.5	—	—	123	34.7	0.30	—	—	1.1	—	—	—	Diuresis 13th day after start of therapy (4/11). Minimum weight following diuresis. A second course of ACTH therapy (5/22-6/6 920 mg.) induced no diuresis. Generalized edema continues 8/17/50.
	3/1-8		—	—	—	—	—	—	—	—	—	—	—	—	—	
	3/29		22.5	—	—	—	—	—	—	—	—	—	—	—	—	
	3/29-4/8	ACTH 880 mg. (11d)	22.5	44.1	—	—	200	27.9	0.22	—	—	1.6	—	—	—	Duration of disease—1 mo. Constant edema with no spontaneous diuresis. Diuresis 11th day after start of therapy (3/15). Minimum weight following diuresis. No manifest edema—8/17/50.
	4/10		22.5	—	—	—	—	—	—	—	—	—	—	—	—	
	4/11		20.5	46.0	—	—	168	25.7	0.27	—	—	1.8	—	—	—	
	4/11		15.0	—	—	—	—	—	—	—	—	—	—	—	—	
	5/8		17.0	43.5	—	—	154	29.4	0.28	—	—	1.5	—	—	—	
M. L. M. Age 3 yrs. Ht. 91.5 cm. Wt. 14.5 kg. S.A. 0.58M <sup>2</sup>	5/26	ACTH 800 mg. (10d)	22.3	—	—	—	211	25.9	0.20	—	—	1.6	—	—	—	Duration of disease—15 mos. Constant edema since onset with no spontaneous diuresis. No diuresis after Cortisone. Diuresis 8th day after start of therapy (4/4). Minimum weight. No manifest edema 8/17/50.
	5/27		25.5	41.2	—	—	—	—	—	—	—	—	—	—	—	
	8/7		—	—	—	—	—	—	—	—	—	—	—	—	—	
	Expected normal value	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	3/2/50	ACTH 800 mg. (10d)	20.7	29.5	—	—	170	20.7	0.17	—	—	1.4	—	—	—	Duration of disease—15 mos. Constant edema since onset with no spontaneous diuresis. No diuresis after Cortisone. Diuresis 8th day after start of therapy (4/4). Minimum weight. No manifest edema 8/17/50.
	3/4		21.4	—	—	—	—	—	—	—	—	—	—	—	—	
	3/4-13		—	—	—	—	—	—	—	—	—	—	—	—	—	
	3/14		23.9	44.2	—	—	198	28.2	0.22	—	—	1.6	—	—	—	
	3/15		21.4	—	—	—	—	—	—	—	—	—	—	—	—	
S. S. M. Age 3 yrs. Ht. 94.0 cm. Wt. 14.5 kg. S.A. 0.60M <sup>2</sup>	3/20	Cortisone 400 mg. (7d)	15.9	43.1	—	—	157	24.7	0.27	—	—	1.7	—	—	—	Duration of disease—15 mos. Constant edema since onset with no spontaneous diuresis. No diuresis after Cortisone. Diuresis 8th day after start of therapy (4/4). Minimum weight. No manifest edema 8/17/50.
	3/22		14.5	—	—	—	—	—	—	—	—	—	—	—	—	
	3/22		—	41.2	—	—	211	25.9	0.20	—	—	1.6	—	—	—	
	Expected normal value	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	2/27/50	ACTH 1040 mg. (13d)	15.0	29.0	—	—	241	16.0	0.12	—	—	1.8	—	—	—	Duration of disease—15 mos. Constant edema since onset with no spontaneous diuresis. No diuresis after Cortisone. Diuresis 8th day after start of therapy (4/4). Minimum weight. No manifest edema 8/17/50.
	3/2-8		—	—	—	—	—	—	—	—	—	—	—	—	—	
	3/9		19.3	41.3	—	—	193	14.0	0.21	—	—	3.0	—	—	—	
	3/23		15.0	17.1	—	—	129	12.0	0.13	—	—	1.4	—	—	—	
	3/27		15.0	—	—	—	—	—	—	—	—	—	—	—	—	
Expected normal value	3/27-4/8	ACTH 1040 mg. (13d)	—	—	—	—	—	—	—	—	—	—	—	—	—	Duration of disease—15 mos. Constant edema since onset with no spontaneous diuresis. No diuresis after Cortisone. Diuresis 8th day after start of therapy (4/4). Minimum weight. No manifest edema 8/17/50.
	4/4		15.6	60.8	—	—	238	17.7	0.26	—	—	3.4	—	—	—	
	4/6		15.6	—	—	—	—	—	—	—	—	—	—	—	—	
	4/9		12.7	34.3	—	—	211	26.1	0.16	—	—	1.3	—	—	—	
	4/11		13.2	42.7	—	—	218	26.8	0.20	—	—	1.6	—	—	—	
	Expected normal value	—	—	—	—	—	—	—	—	—	—	—	—	—	—	

in the  $C_{IN}:C_{PAH}$  ratio are associated with vascular changes or alterations in the permeability of the glomerular membrane cannot be assessed at present.

#### *Maximum tubular excretion of PAH*

Increases in  $T_{MPAH}$  accompanied increases in  $C_{IN}$  in two children (M. L. and S. S.) in whom it was measured before and during diuresis. The changes in  $T_{MPAH}$  were less than those in  $C_{IN}$  so that the  $C_{IN}:T_{MPAH}$  ratios increased from initially low values before to higher values. In the remaining child in whom repeated measurements of  $T_{MPAH}$  were made, no change in  $C_{IN}$  was observed and the changes in  $T_{MPAH}$  were irregular.

#### *Plasma and blood volume*

Increases in plasma volume during or after diuresis were observed in four out of five children in whom such observations were made. The changes in I. C., K. N., B. B., and J. S. were 29, 17, 26, and 11% respectively, above the control values. Corresponding increases in blood volume in I. C., K. N., and J. S. were observed but the changes were proportionately less because of decreases in hematocrit values. Failure to observe an increase in plasma volume in R. K. may possibly be explained again by a failure to make the measurement at the proper time.

#### DISCUSSION

Prompt increases above initially reduced rates of glomerular filtration are commonly seen during the early stages of acute nephritis in children. On the other hand, reduced clearances in children with the nephrotic syndrome of several months' duration have been interpreted as indicating a less reversible process. The rapid increases in glomerular filtration rate reported here in children who had reduced kidney function and who were given ACTH demonstrate, therefore, a potentiality for improvement in function beyond that commonly considered possible in children with the nephrotic syndrome.

There is no evidence and it is not implied that these results are peculiar to diureses induced by ACTH. Although the magnitude of the changes was somewhat greater than those previously reported with other agents (1, 4, 19), it is entirely

possible and probable that quantitatively similar changes may accompany spontaneous or induced diureses.

The results described have no bearing on the question of whether pituitary or adrenal cortical hormones have any direct relationship to the nephrotic syndrome. They do indicate that ACTH administration may induce repeated diureses at predictable times permitting serial measurements of changes which may accompany and be involved in the mechanism of diuresis. Thus large increases in glomerular filtration rate and significant increases in plasma volume were observed during diureses in these children. These observations lend support to the concept (20) that increases in plasma volume and in glomerular filtration rate accompany and may be involved in the mechanism of diuresis in children with the nephrotic syndrome.

#### SUMMARY

Profuse, sustained diureses occurring at predictable times in a high percentage of trials during or following administration of ACTH to children with the nephrotic syndrome permitted observations on changes which may accompany and be involved in the mechanism of diuresis. Serial measurements of discrete kidney functions and plasma volume are reported before, during and after 13 such diureses in eight children. The results indicate:

1. In five children with initially reduced rates of glomerular filtration, increases in inulin clearances ranging from 50 to 256% above control values were observed during or following diureses on five out of six occasions. In three observations on three children with rates of glomerular filtration initially within the normal range, an increase of 54% was observed in one. Thus in nine observations where inulin clearances were measured before and after the outset of diuresis, significant increases were observed in six.

2. Daily 24-hour creatinine clearances, measured in one of the three instances in which no marked increase in inulin clearance was observed *after* diuresis, suggest that glomerular filtration rate did increase *during* diuresis. In addition, the 24-hour clearances suggest that a marked increase in glomerular filtration rate during diuresis may be followed by a decrease from the maximum



value, but with subsequent stabilization at a value slightly or markedly above the control. Repeated responses in children with reduced function may then be associated with a progressive increase to normal or even "supernormal" values.

3. A consistent decrease in the endogenous creatinine: inulin clearance ratio was observed as glomerular filtration rate increased. However, clearances of thiosulfate and inulin showed reasonably good agreement at both high and low rates of glomerular filtration.

4. Clearances and maximum tubular excretion of p-aminohippurate increased during diuresis but proportionately less than inulin clearances. Consequently, increases in the  $C_{IN}:C_{PAH}$  and the  $C_{IN}:T_{M_{PAH}}$  ratios were observed as rates of glomerular filtration increased.

5. In four of five observations on five children, increases in plasma volume (T-1824) ranging from 11 to 29% above control values were observed during diureses.

#### CONCLUSIONS

1. Diureses occurring during or following administration of ACTH to children with the nephrotic syndrome are usually associated with marked improvement in kidney function. Repeated diureses in children with initially reduced function may be associated with progressive increases in rates of glomerular filtration to normal values. These observations demonstrate a potentiality for improvement in function beyond that commonly considered possible in the nephrotic syndrome of many months' duration. It is believed that these changes are not peculiar to diureses associated with ACTH administration but may accompany spontaneous or other types of induced diureses.

2. The changes observed in plasma volume and glomerular filtration rate support the concept that increases in plasma volume and glomerular filtration rate are associated with the mechanism of diuresis in children with the nephrotic syndrome.

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