JCI The Journal of Clinical Investigation

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

Henry L. Barnett, … , Helen McNamara, Wallace W. McCrory

J Clin Invest. 1951;30(2):227-235. https://doi.org/10.1172/JCI102437.

Research Article

Find the latest version:

https://jci.me/102437/pdf

THE EFFECT OF ADRENOCORTICOTROPHIC HORMONE ON CHILDREN WITH THE NEPHROTIC SYNDROME. II. PHYSIOLOGIC OBSERVATIONS ON DISCRETE KIDNEY FUNCTIONS AND PLASMA VOLUME [1]

By HENRY L. BARNETT, CAROLYN W. FORMAN,[2] HELEN McNAMARA, and WALLACE W. McCRORY [3]

(From The New York Hospital and the Department of Pediatrics, Cornell University Medical College, New York City)

And

By MILTON RAPOPORT, ALEXANDER J. MICHIE, and GUILIO BARBERO

(From The Children's Hospital of Philadelphia and the Department of Pediatrics, and Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia)

(Submitted for publication September 12, 1950; accepted, December 4, 1950)

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 [4] 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

[1] Presented in part before the Society of Pediatric Research at French Lick, Indiana, on May 9, 1950.

[2] Public Health Service Postdoctorate Fellow, 1949–51.

[3] Lewis Cass Ledyard, Jr. Fellow in Pediatrics, 1949–50. Present address: Children's Hospital of Philadelphia.

[4] 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).

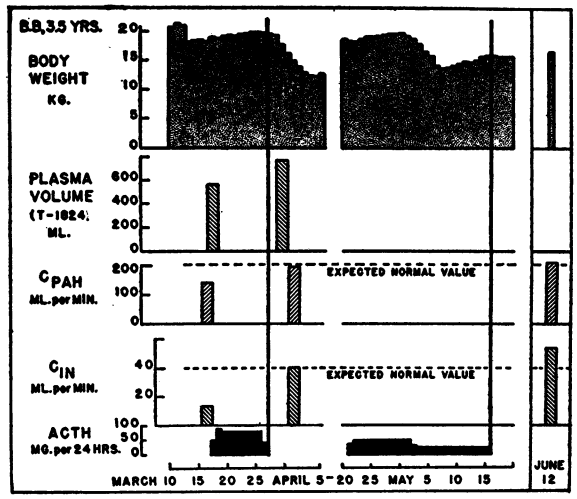

FIG. 1. RELATION OF CHANGES IN BODY WEIGHT, PLASMA VOLUME, AND CLEARANCES OF INULIN AND P-AMINOHIPPURATE TO ADMINISTRATION OF ACTH IN A CHILD WITH THE NEPHROTIC SYNDROME

RESULTS [5]

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. [6] 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, measurements 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.[7]

[5] 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.

[6] Only a small fraction of the observed increases in C_{IN} could be related to increases in rate of urine flow during diuresis.

[7] 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.

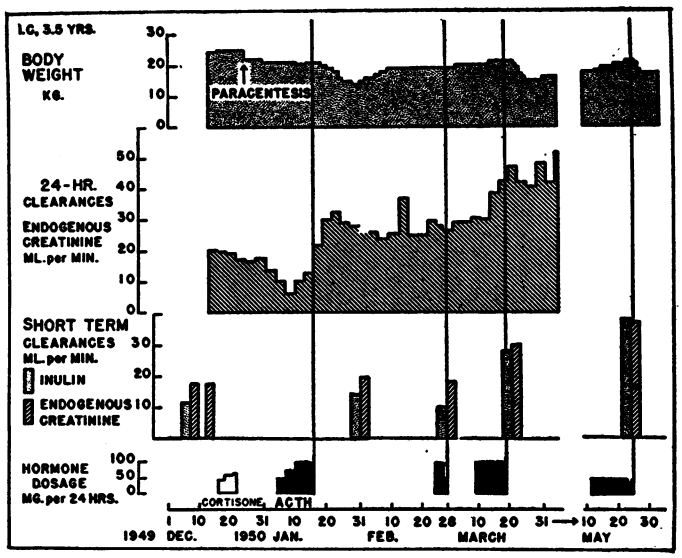

FIG. 2. RELATION OF CHANGES IN BODY WEIGHT AND CLEARANCES OF INULIN AND ENDOGENOUS CREATININE TO ADMINISTRATION OF ACTH IN A CHILD WITH THE NEPHROTIC SYNDROME

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.[8] 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 associated, 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

[8] 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.

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

The New York Hospital

Subject	Date	Hormone administration	Weight	C_{IN}	C_{CR}	C_{THIO}	C_{PAH}	T_{MPAH}	C_{IN}/C_{PAH}	C_{CR}/C_{IN}	C_{THIO}/C_{IN}	C_{IN}/T_{MPAH}	Plasma volume	Blood volume	Hematocrit	Comment
			kg.	*ml. per min.*	*ml. per min.*	*ml. per min.*	*ml. per min.*	*mg. per min.*					*ml.*	*ml.*	%	
I. C.	12/7/49		23.4	11.9	18.0	12.0	77.9	—	0.15	1.5	1.0	—				Duration of disease—7 mos.
F. Age 3.5 yrs.	12/12		24.4	—	18.0	—	—	—	—	—	—	—				Constant edema since outset with no spontaneous diuresis.
Ht. 96.0 cm.	12/16–21	Cortisone 335 mg. (6d)	24.7–25.2	—	—	—	—	—	—	—	—	—				
Wt. 15.2 kg.‡	1/4/50		21.4	—	—	—	—	—	—	—	—	—				
S.A. 0.62M²	1/4–16	ACTH 1000 mg. (13d)†	21.4–20.9	—	—	—	—	—	—	—	—	—				
	1/19		20.3	—	—	—	—	—	—	—	—	—				‖Diuresis 15th day after start of therapy (1/19).
	1/30		14.2	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	2/1		14.6	14.3	19.9	12.8	—	—	—	1.4	0.9	—				Outset of reaccumulation of edema.
	2/16		19.6	—	—	—	—	—	—	—	—	—				Maximum weight.
	2/23		19.1	—	—	—	—	—	—	—	—	—				
	2/24–27	ACTH 350 mg. (3½d)	18.5–19.1	—	—	—	—	—	—	—	—	—				No diuresis.
	2/28		19.3	10.1	18.6	—	70.9	—	0.14	1.8	—	—				
	3/7		19.6	—	—	—	—	—	—	—	—	—	663	1074	40.0	
	3/8–17	ACTH 950 mg. (9½d)	19.6–21.4	—	—	—	—	—	—	—	—	—				
	3/21		20.9	28.2	30.4	—	119	—	0.24	1.1	—	—				Diuresis 13th day after start of therapy (3/21)
	3/22		20.0	—	—	—	—	—	—	—	—	—	853	1218	31.4	
	3/27		15.0	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	3/30		15.4	—	—	—	—	—	—	—	—	—				Outset of reaccumulation of edema.
	5/10		17.5	—	—	—	—	—	—	—	—	—				
	5/11–24	ACTH 687.5 mg. (14d)	17.2–20.7	—	—	—	—	—	—	—	—	—				
	5/24		20.7	38.2	37.5	33.2	106	—	0.36	1.0	—	—				
	5/26		20.1	—	—	—	—	—	—	—	—	—				Diuresis 15th day after start of therapy (5/26).
	11/16		17.5	—	—	—	—	—	—	—	—	—				In apparent clinical remission 12/1/50.
Expected normal value §				*44.1*			*225*		*0.20*							
K. N.	1/20/50		20.5	8.1	16.6	—	71.9	—	0.11	2.0	—	—				Duration of disease—10 mos.
M. Age 3 yrs.	1/20–27	ACTH 675 mg. (8d)	20.5–20.6	—	—	—	—	—	—	—	—	—				Constant edema since outset with no spontaneous diuresis.
Ht. 91.5 cm.	1/29		20.3	—	—	—	—	—	—	—	—	—				Diuresis 9th day after start of therapy (1/29).
Wt. 14.1 kg.	2/3		14.3	25.2	30.1	—	94.2	—	0.27	1.2	—	—				
S.A. 0.58M²	2/6		12.2	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	2/9		12.5	—	—	—	—	—	—	—	—	—				Outset of reaccumulation of edema.
	3/3		18.4	—	—	—	—	—	—	—	—	—	553	819	34.0	Maximum weight.
	3/4–13	ACTH 950 mg. (9½d)	18.3–17.4	—	—	—	—	—	—	—	—	—				
	3/10		19.7	—	—	—	—	—	—	—	—	—				Diuresis 6th day after start of therapy (3/10).
	3/11		19.1	—	—	—	—	—	—	—	—	—				
	3/13		17.4	—	—	—	—	—	—	—	—	—	645	904	30.0	
	3/18		12.4	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	3/21		12.9	—	—	—	—	—	—	—	—	—				Outset of reaccumulation.
	4/20		15.9	—	—	—	—	—	—	—	—	—				
	4/21		16.2	—	—	—	—	—	—	—	—	—				Maximum weight.
	4/21–5/1	ACTH 537.5 mg. (11d)	16.2–15.4	—	—	—	—	—	—	—	—	—				Diuresis 8th day after start of therapy (4/29).
	4/29		17.2	—	—	—	—	—	—	—	—	—				
	4/30		16.6	—	—	—	—	—	—	—	—	—				
	4/31		16.1	—	—	—	—	—	—	—	—	—				
	5/4		13.9	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	5/31		16.1	27.6	38.2	—	79.8	—	0.35	1.4	—	—				
	11/17		15.5	—	—	—	—	—	—	—	—	—				In apparent clinical remission 12/1/50.
Expected normal value				*41.2*			*211*		*0.20*							No manifest edema.

* 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:

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

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 I—*Continued*

Subject	Date	Hormone administration	Weight	C_{IN}	C_{CR}	C_{THIO}	C_{PAH}	$T_{M_{PAH}}$	C_{IN}/C_{PAH}	C_{CR}/C_{IN}	C_{THIO}/C_{IN}	$C_{IN}/T_{M_{PAH}}$	Plasma volume	Blood volume	Hematocrit	Comment
			kg.	*ml. per min.*	*ml. per min.*	*ml. per min.*	*ml. per min.*	*mg. per min.*					*ml.*	*ml.*	%	
B. B.	3/16/50		18.3	14.0	28.1	16.2	148	—	0.09	2.0	1.2	—		—		Duration of disease—7 mos.
F. Age 3.5 yrs.	3/17		19.0	—	—	—	—	—	—	—	—	—	615	814	25.6	Constant edema since outset with no spontaneous diuresis.
Ht. 90.0 cm.	3/17–26	ACTH 740 mg. (9d)	19.0–19.8	—	—	—	—	—	—	—	—	—				
Wt. 13.7 kg.	3/28		19.3	—	—	—	—	—	—	—	—	—				Diuresis 11th day after start of therapy (3/28).
S.A. 0.57M²	3/29		17.7	—	—	—	—	—	—	—	—	—	774			
	3/31		14.8	40.6	44.5	39.0	197	—	0.21	1.1	1.0	—				
	4/3		12.4	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	4/20		18.6	—	—	—	—	—	—	—	—	—				Maximum weight.
	4/21		18.4	—	—	—	—	—	—	—	—	—				
	4/21–5/15	ACTH 893.8 mg. (25d)	18.4–15.9	—	—	—	—	—	—	—	—	—				
	5/1		19.1	—	—	—	—	—	—	—	—	—				Diuresis 10th day after start of therapy (5/1).
	5/7		13.6	—	—	—	—	—	—	—	—	—				Minimum weight following therapy.
	5/9		14.1	—	—	—	—	—	—	—	—	—				In apparent clinical remission 5/9–10/1.
	6/12		16.5	54.0	55.7	—	211	—	0.26	1.0	—	—				Reaccumulation of edema 10/1/50.
	11/2		18.2	—	—	—	—	—	—	—	—	—				13 days ACTH therapy (525 mg.) resulted in diuresis.
Expected normal value				*40.5*			*207*		*0.20*							
J. S.	3/6/50		13.9	41.2	57.9	46.3	196	—	0.21	1.4	1.1	—				Duration of disease—2.5 mos.
M. Age 3.2 yrs.	4/11		15.3	45.8	58.6	—	196	—	0.23	1.3	—	—				One spontaneous diuresis 4 weeks after outset.
Ht. 95.0 cm.	4/12			—	—	—	—	—	—	—	—	—	678	1064	38.0	Minimal edema at start of therapy.
Wt. 15.0 kg.	4/14–20	ACTH 625 mg. (6½d)	15.6–15.9	—	—	—	—	—	—	—	—	—				
S.A. 0.61M²	4/21		15.7	—	—	—	—	—	—	—	—	—	750	1143	36.0	
	4/22		15.2	42.8	46.4	—	193	—	0.22	1.1	—	—				Diuresis 8th day after start of therapy (4/22).
	4/24		14.7	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	8/31		18.0	—	—	—	—	—	—	—	—	—				
Expected normal value				*45.5*			*221*		*0.20*							Moderate intermittent peripheral edema 12/1/50.
R. K.																
F. Age 3.9 yrs.	7/10/50		27.4	37.1	48.1	—	212	—	0.18	1.3	—	—				Duration of disease—11 mos.
Ht. 100 cm.	7/11		27.8	—	—	—	—	—	—	—	—	—	933	1510	40.0	One diuresis in March 1950 following paracentesis.
Wt. 16.1 kg.	7/12		27.6	—	—	—	—	—	—	—	—	—				Reaccumulation of edema 4 months later.
S.A. 0.64M²	7/12–22	ACTH 500 mg. (11d)	27.6–27.8	—	—	—	—	—	—	—	—	—				
	7/23		27.2	—	—	—	—	—	—	—	—	—				Diuresis 11th day after start of therapy (7/23).
	7/27		19.3	56.0	64.5	—	233	—	0.24	1.2	—	—	918	1463	39.0	
	8/1		17.2	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
	11/26		21.8	—	—	—	—	—	—	—	—	—				Reaccumulation of edema and spontaneous diuresis in October and again in November.
Expected normal value				*45.5*			*233*		*0.20*							

TABLE I—*Continued*

Children's Hospital of Philadelphia

Subject	Date	Hormone administration	Weight	C_{IN}	C_{CR}	C_{THIO}	C_{PAH}	T_{MPAH}	C_{IN}/C_{PAH}	C_{CR}/C_{IN}	C_{THIO}/C_{IN}	C_{IN}/T_{MPAH}	Plasma volume	Blood volume	Hematocrit	Comment
			kg.	*ml. per min.*	*ml. per min.*	*ml. per min.*	*ml. per min.*	*mg. per min.*					*ml.*	*ml.*	%	
R. T.	1/4/50		17.5	49.4	—	—	160	31.3	0.31	—	—	1.6				Duration of disease—4 mos.
M. Age 3 yrs.	1/6–22	Cortisone 1300 mg. (17d)	—	—	—	—	—	—	—	—	—	—				Constant edema since outset with no spontaneous diuresis.
Ht. 91.5 cm.	1/16		20.0	45.1	—	—	220	39.0	0.21	—	—	1.2				No diuresis following Cortisone.
Wt. 14.1 kg.	2/20		16.8	37.5	—	—	123	34.7	0.30	—	—	1.1				
S.A. 0.58M²	3/1–8	Cortisone 575 mg. (8d) DCA 40 mg.		—	—	—	—	—	—	—	—	—				No diuresis.
	3/29		22.5	—	—	—	—	—	—	—	—	—				
	3/29–4/8	ACTH 880 mg. (11d)		—	—	—	—	—	—	—	—	—				
	4/10		22.5	44.1	—	—	200	27.9	0.22	—	—	1.6				
	4/11		22.5	—	—	—	—	—	—	—	—	—				Diuresis 13th day after start of therapy (4/11).
	4/14		20.5	46.0	—	—	168	25.7	0.27	—	—	1.8				Minimum weight following diuresis.
	4/15		15.0	—	—	—	—	—	—	—	—	—				
	5/8		17.0	43.5	—	—	154	29.4	0.28	—	—	1.5				A second course of ACTH therapy (5/22–6/6 920 mg.) induced no diuresis.
	5/26		22.3	—	—	—	—	—	—	—	—	—				
	8/7		25.5	—	—	—	—	—	—	—	—	—				Generalized edema continues 8/17/50.
Expected normal value				*41.2*			*211*	*25.9*	*0.20*			*1.6*				
M. L.	3/2/50		20.7	29.5	—	—	170	20.7	0.17	—	—	1.4				Duration of disease—1 mo.
	3/4		21.4	—	—	—	—	—	—	—	—	—				Constant edema with no spontaneous diuresis.
M. Age 3 yrs.	3/4–13	ACTH 800 mg. (10d)	—	—	—	—	—	—	—	—	—	—				
Ht. 91.5 cm.	3/14		23.9	44.2	—	—	198	28.2	0.22	—	—	1.6				
Wt. 14.1 kg.	3/15		21.4	—	—	—	—	—	—	—	—	—				Diuresis 11th day after start of therapy (3/15).
S.A. 0.58M²	3/20		15.9	43.1	—	—	157	24.7	0.27	—	—	1.7				
	3/22		14.5	—	—	—	—	—	—	—	—	—				Minimum weight following diuresis.
Expected normal value				*41.2*			*211*	*25.9*	*0.20*			*1.6*				No manifest edema—8/17/50.
S. S.	2/27/50		15.0	29.0	—	—	241	16.0	0.12	—	—	1.8				Duration of disease—15 mos.
M. Age 3.5 yrs.	3/2–8	Cortisone 400 mg. (7d)	—	—	—	—	—	—	—	—	—	—				Constant edema since outset with no spontaneous diuresis.
Ht. 94.0 cm.	3/9		19.3	41.3	—	—	193	14.0	0.21	—	—	3.0				
Wt. 14.5 kg.	3/23		15.0	17.1	—	—	129	12.0	0.13	—	—	1.4				No diuresis after Cortisone.
S.A. 0.60M²	3/27		15.0	—	—	—	—	—	—	—	—	—				
	3/27–4/8	ACTH 1040 mg. (13d)	—	—	—	—	—	—	—	—	—	—				
	4/4		15.6	—	—	—	—	—	—	—	—	—				Diuresis 8th day after start of therapy (4/4).
	4/6		15.6	60.8	—	—	238	17.7	0.26	—	—	3.4				
	4/9		12.7	—	—	—	—	—	—	—	—	—				Minimum weight.
	4/11		13.2	34.3	—	—	211	26.1	0.16	—	—	1.3				
Expected normal value				*42.7*			*218*	*26.8*	*0.20*			*1.6*				No manifest edema 8/17/50.

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.

ACKNOWLEDGMENTS

We are indebted to Flora Hurwitz, R.N., Marie Ragni, B.A., Jean Tracy, R.N., and Josephine Codis, R. N., for nursing and technical assistance.

REFERENCES

1. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L., Treatment of nephrosis with concentrated human serum albumin. II. Effects on renal function and on excretion of water and some electrolytes. J. Clin. Invest., 1950, **29**, 896.
2. Rosenblum, A. H., Lander, H. B., and Fisher, R. M., Measles in the nephrotic syndrome. J. Pediat., 1949, **35**, 574.
3. Fox, C. L., Jr., and McCune, D. J., Electrolyte changes in nephrosis. Occurrence of diuresis following administration of sodium and potassium salts. Am. J. M. Sc., 1948, **216**, 1.
4. Chasis, H., Goldring, W., and Baldwin, D. S., Effect of febrile plasma, typhoid vaccine, and nitrogen mustard on renal manifestations of human glomerulonephritis. Proc. Soc. Exper. Biol. & Med., 1949, **71**, 565.
5. Farnsworth, E. B., Metabolic changes associated with administration of adrenocorticotropin in the nephrotic syndrome. Proc. Soc. Exper. Biol. & Med., 1950, **74**, 60.
6. Rapoport, M., Michie, A., Barbero, G., Barnett, H. L., Forman, C. W., McNamara, H., and McCrory, W. W., The effect of adrenocorticotrophic hormone on children with the nephrotic syndrome. I. Clinical observations. In preparation.
7. McNamara, H., Barnett, H. L., Forman, C. W., McCrory, W. W., and Lauson, H. D., The effect of ACTH on children with the nephrotic syndrome. III. Observations on distribution and excretion of water, electrolytes, and nitrogen. In preparation.
8. Barnett, H. L., Hare, K., McNamara, H., and Hare, R., Measurement of glomerular filtration rate in premature infants. J. Clin. Invest., 1948, **27**, 691.
9. Hare, R. S., Endogenous creatinine in serum and urine. Proc. Soc. Exper. Biol. & Med., 1950, **74**, 148.
10. Newman, E. V., Gilman, A., and Philips, F. S., The renal clearance of thiosulfate in man. Bull. Johns Hopkins Hosp., 1946, **79**, 229.
11. Chinard, F. P., and Eder, H. A., The determination of the concentration of the dye T-1824 in normal and lipemic plasmas. J. Exper. Med., 1948, **87**, 473.
12. Smith, C. H., A method for determining the sedimentation rate and red cell volume in infants and children with the use of capillary blood. Am. J. M. Sc., 1936, **192**, 73.
13. Woodbury, R. M., Statures and weights of children under six years of age. U. S. Labor Dept. Children's Bureau Publication, No. 87, 1922.
14. DuBois, E. F., Basal Metabolism in Health and Disease. Lea & Febiger, Philadelphia, 3rd edition, 1936, p. 135.
15. Smith, H. W., Kidney: Structure and Function in Health and Disease. Oxford University Press, New York. In press.

16. Barnett, H. L., Kidney function in young infants. Pediatrics, 1950, **5**, 171.
17. Hare, K., Goldstein, H., Barnett, H. L., McNamara, H., and Hare, R. S., Renal excretion of creatinine in man. Federation Proc., 1949, **8**, 67.
18. Sirota, J. H., Baldwin, D. S., and Villarreal, H., Diurnal variations of renal function in man. J. Clin. Invest., 1950, **29**, 187.
19. Cargill, W. H., Effect of the intravenous administration of human serum albumin on renal function. Proc. Soc. Exper. Biol. & Med., 1948, **68**, 189.
20. Eder, H. A., Chinard, F. P., Greif, R. L., Cotzias, G. C., Hiller, A., Van Slyke, D. D., and Lauson, H. D., A study of the changes in plasma volume, renal function, and water and salt balance induced by repeated administration of human plasma albumin to patients with the nephrotic syndrome. J. Clin. Invest., 1948, **27**, 532.