THE EFFECT OF CORTICOTROPIN (ACTH) ON GLOMERULAR PERMEABILITY TO ALBUMIN IN CHILDREN WITH THE NEPHROTIC SYNDROME [1, 2]

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Present evidence indicates that proteinuria in patients with the nephrotic syndrome is the result of increased permeability of the glomerular capillary walls to proteins, particularly to albumin (1, 2). A rough indication of the permeability to albumin, relative to permeability to water, is provided by the ratio of the concentration of albumin in glomerular fluid to that in plasma. Assuming that no albumin is excreted by the tubules, the rate of albumin excretion (in mg. per min.) divided by the rate of glomerular filtration of water (GFR, in ml. per min.) represents the lowest possible concentration of albumin in glomerular fluid (in mg. per ml.); if some albumin is reabsorbed by the tubules, as seems likely, the actual concentration of albumin in glomerular fluid would be greater than this calculated value. If it is accepted that the clearance of inulin (C_{IN}) is equivalent to GFR in children with the nephrotic syndrome (3), it follows that the renal clearance of albumin (C_{ALB}) divided by C_{IN}, *i.e.*, C_{ALB}/C_{IN}, represents the minimum ratio of the albumin concentration in glomerular fluid to that in plasma.

Chinard, Lauson, and Eder (4) showed that in patients with the nephrotic syndrome the renal clearance of the blue dye, T-1824 (C_{T-1824}), was somewhat less than but approximately proportional to C_{ALB}. It would appear, therefore, that where large changes in permeability are expected C_{T-1824} should be a satisfactory substitute for C_{ALB}. The methods for determining concentrations of the dye in serum and urine (4) are much easier than the immunochemical method for albumin (1, 5).

In many patients with the nephrotic syndrome, proteinuria diminished during or after treatment with corticotropin (ACTH) or Cortisone (6–17). Further, in most patients so treated GFR increased (6–8, 12). These observations suggested that glomerular permeability to albumin decreased under the influence of treatment. The present study was undertaken to estimate the order of magnitude of this change in permeability. A preliminary report of this work has been previously published (18).

METHODS

A. *Patients.* Clinical data are summarized in Table I. All patients received ACTH intramuscularly every six hours in the dosage indicated. One child, F. deK., had had no edema for several years; as measured by the urea clearance, renal function had remained about 40 per cent of normal during those years. Proteinuria varied between 1 and 2 Gm. per 24 hours in this patient prior to treatment with ACTH.

B. *Procedures.* Clearances of T-1824 (C_{T-1824}), specific endogenous creatinine (C_{CR}), inulin (C_{IN}) and p-aminohippurate (C_{PAH}) and the plasma volume were estimated before, during, and after courses of ACTH. Food and fluids were withheld for at least 12 hours before each test. The procedure followed in most observations was as follows: Beginning about 8 a.m., a control urine specimen (U_0) was obtained through an indwelling catheter. The bladder was washed out only with air. A control blood specimen was taken (B_0). Pipetted 2 or 3 ml. aliquots of 0.5 per cent T-1824 were then injected intravenously by the method of Barnett and Fellers (19). After 10 minutes a venous blood sample was withdrawn (B_1). Another aliquot of dye was delivered by the same pipette into a volumetric flask, the volume of which was roughly one-fifth of the expected plasma volume. This, filled to the mark with physiologic saline, was the "reference solution" (20). Several minutes later the bladder was washed out with air and the urine saved for total protein determination in most observations. The urine

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for estimation of C_{T-1824} (U_1) was collected 10 to 31 minutes later; another blood sample (B_2) was taken soon thereafter. Priming doses of inulin and PAH were next injected intravenously, and a sustaining infusion of these substances in physiologic saline was administered at a rate of 0.5 ml. per min. by means of a Bowman constant infusion pump. After an equilibration period of about one hour, three urine collections were made, each of 10 to 20 minutes duration (U_{2-4}); blood was withdrawn before U_2 and after U_4. Concentrations of inulin and of PAH in plasma in the several patients ranged between 27 and 109 and between 0.5 and 3.3 mg. per 100 ml., respectively. C_{CR} was calculated for all periods, C_{T-1824} for U_1, and C_{IN} and C_{PAH} for U_{2-4}. The presence of inulin in high concentration made it impossible to clarify most of the urines by centrifugation and therefore interfered with the determination of dye concentration. It was for this reason that C_{T-1824} was measured prior to administration of inulin. To estimate C_{T-1824}/C_{IN}, the ratio C_{T-1824}/C_{CR} for period U_1 was multiplied by the average C_{CR}/C_{IN} ratio obtained during the subsequent periods U_{2-4}. Similarly, to estimate total protein excretion/C_{IN}, the ratio of total protein excretion/C_{CR} for the period preceding U_1 was multiplied by the average C_{CR}/C_{IN} ratio.

C. *Analytical methods. Inulin* concentration in cadmium filtrates (21) of serum and in suitably diluted urine was determined by the method of Schreiner (22). Omitting precipitation of protein in these urines introduced no error in the inulin determination of more than 2 per cent. The concentration of *PAH,* also in cadmium filtrates of serum and diluted, unprecipitated urine, was determined by a modification of the method of Bratton and Marshall (21).

Specific endogenous creatinine was determined by a modification of the method of Hare (23). In the earlier cases, serum protein was precipitated (1:5) by the tungstic acid method of Wu (24), and the urine protein was not precipitated. Later, the proteins of both serum and urine were precipitated (1:5) by trichloroacetic acid. Ten ml. aliquots of serum filtrates and of diluted urine, as well as the standard solutions of creatinine zinc chloride, were all made up to contain 5 per cent trichloroacetic acid. One ml. of saturated oxalic acid and approximately 40 mg. of Lloyd's reagent were added. After frequent shaking during a 10-minute period the solution was centrifuged and the supernate carefully aspirated. The creatinine adsorbed to Lloyd's reagent was eluted by adding 5 ml. of alkaline picrate (Hare's formula [23]) and shaking frequently during a 10-minute period. After centrifugation the clear supernate was transferred with a Wintrobe pipette to an 18 × 150 mm. cuvette; the optical density was read in a Coleman Model 6A clinical spectrophotometer at a wave length setting of 500 mμ. A portion of the light aperture of the cuvette holder was blocked off by black cellophane tape. By eluting the creatinine from 10 ml. of serum filtrate into 5 ml. of alkaline picrate an additional two-fold concentration was achieved (in effect, the serum creatinine was diluted only 1:2.5). Thus the very low concentrations frequently encountered in small children (*i.e.,* as little as 0.15 to 0.20 mg. per 100 ml. of serum) could be estimated with satisfactory accuracy. The concentrations in two or three successive serum samples were averaged and this average value was used in calculating C_{CR} for all periods.

T-1824 in the serum was estimated by the acetone extraction procedure of Chinard and Eder (20). The concentration of dye in urine clarified by centrifugation was determined by a modification of the method of Chinard, Lauson, and Eder (4). All urines were buffered with 0.5 ml. of M phosphate buffer, pH 7.0, and if necessary diluted with physiologic saline. Final volumes varied from 2 to 5 ml. Because the urinary blank was often relatively large, and because the dye excretion was usually quite low after ACTH, several "corrections" were made to secure maximum accuracy in calculating C_{T-1824}. Optical density was read both at 620 mμ and 450 mμ, the instrument being set to zero optical density with a control solution of saline and buffer.[5] The "corrected" optical density at 620 mμ of U_1 in the *pre-ACTH study* was calculated by the equation:

$$\text{"corrected" } D_{620} = \frac{\text{observed } D_{620} - K_1 \times \text{observed } D_{450}}{1 - K_1/K_2},$$

where D_{620} and D_{450} are the optical density of U_1 at 620 mμ and 450 mμ, respectively; K_1 is the optical density at $\lambda = 620$ mμ of the control urine (U_0) of the pre-ACTH study divided by its optical density at $\lambda = 450$ mμ; K_2 is the *increment* in optical density at $\lambda = 620$ mμ divided by that at $\lambda = 450$ mμ due to addition of a known amount of dye to U_0 (*i.e.,* the optical density of U_0 at each wavelength was subtracted from that of [U_0 + dye]). "Corrected" concentration in U_1 was calculated as:

$$\text{"Corrected" concentration} = \frac{\text{"corrected" } D_{620} \text{ (of } U_1)}{D_{620} \text{ (of } U_0 + \text{dye)} - D_{620} \text{ (of } U_0)} \times \text{concentration of dye in } (U_0 + \text{dye}) \times \text{dilution factor of } U_1.$$

"Corrected" dye excretion is the product of the concentration and urine flow.[6]

[5] Under the conditions of the studies reported here the molar concentration ratios of albumin to dye in the plasma, and therefore also in the glomerular filtrate, were well within the range of 1:1 to 1:100. Therefore, it may reasonably be assumed that variations in the absorption coefficient of the dye in the urines were relatively unimportant (4).

[6] An example will make clear how these corrections were applied. In patient W. H. (2-7-51), the optical densities of U_0 and U_1 at $\lambda = 620$ mμ were 0.013 and 0.270, respectively; at $\lambda = 450$ mμ, optical densities of U_0 and U_1 were 0.071 and 0.099, respectively. The optical density of (U_0 + dye) at $\lambda = 620$ mμ was 0.449 and at $\lambda = 450$ mμ was 0.125. Therefore, $K_1 = \frac{0.013}{0.071} = 0.183$; $K_2 = \frac{0.449 - 0.013}{0.125 - 0.071} = 8.02$; $K_1/K_2 = \frac{0.183}{8.02} = 0.023$. The concentration of dye in (U_0 + dye) was 10.0 μg. per

In the *subsequent* studies on each patient, there was often a small residual excretion of T-1824, due to dye administered during the preceding study.[7] For this reason, additional calculations were necessary. K_1 of the *first* study was inserted in the equation and the "corrected" D_{620} and concentration were calculated for U_0 as well as U_1. Multiplying the concentrations (in μg. per ml.) by the respective urine flow rates, V (in ml. per min.), the corrected excretion rates, UV, for T-1824 were obtained (in μg. per min.). To reduce errors which might have arisen from improper bladder emptying or change in GFR, the following calculation was made:

$$\text{"Corrected"}\ (U_{T-1824}V)_{U_1} = \left[\left(\frac{U_{T-1824}V}{C_{CR}}\right)_{U_1} - \left(\frac{U_{T-1824}V}{C_{CR}}\right)_{U_0}\right](C_{CR})_{U_1}.$$

To calculate C_{T-1824}, the "corrected" excretion rate was divided by the concentration in serum interpolated at the midpoint of U_1 from a semi-logarithmic plot of the concentrations in the serum of B_1 and B_2. The optical density of the control serum (B_0) of the same day was subtracted from that of the two dye-stained sera. Usually this correction was negligible (less than 0.003 optical density units).

Plasma and whole blood volumes were calculated in the manner described by Chinard and Eder (20).

Total protein concentration in the urine of the control period immediately preceding U_1 was determined by the biuret method of Hiller, Greif, and Beckman (25). In a few cases, the *clearance of albumin* and C_{T-1824} were estimated concurrently to learn if the proportionality observed by Chinard, Lauson, and Eder (4) obtained under the conditions of the present studies, *i.e.*, during or after ACTH therapy. The immunochemical method used to estimate albumin concentration in urine and plasma was essentially that described by Kunkel and Ward (5). In the present investigation, however, twice-crystallized human plasma albumin was used as the antigen.[8]

RESULTS

The data are summarized in Tables I and II and Figure 1.

Inulin clearance

The inulin clearance rose at least slightly in most of the patients either during or, more often, after the ACTH treatment as reported previously by other workers (7, 8, 12). When initially subnormal, this function often rose to normal; if initially normal, it tended to become supernormal.

Creatinine clearance

As was first shown by Miller and Winkler (26) and subsequently confirmed by others (3, 8, 27), the specific endogenous creatinine clearance exceeded the inulin clearance before ACTH treatment; the highest value of the ratio, C_{CR}/C_{IN}, was 2.65. During and after ACTH therapy, usually in association with a rise in both clearances, the ratio decreased toward the normal value of 1.0 as described previously (8).

T-1824 clearance

In all patients, the dye clearance decreased markedly during and after treatment whether the inulin clearance increased or not. Expressed as the ratio, C_{T-1824}/C_{IN}, the effect was striking; in all but two cases the decrease was 10-fold or more.

Comparison of simultaneously measured clearances of T-1824 and albumin

The data are summarized in Table II. Technical difficulties were encountered in the immunochemical determination of albumin. Furthermore, the very low urinary concentrations of albumin and dye in the post-ACTH periods undoubtedly re-

ml.; U_1 had been diluted 1:4. Urine flow during U_1 was 0.136 ml. per min. The "corrected" optical density of U_1 at $\lambda = 620\ m\mu$ therefore was: $D_{620} = \frac{0.270 - 0.183 \times 0.099}{1 - 0.023}$ = 0.258. The "corrected" concentration of dye in U_1 was: "corrected" concentration $= \frac{0.258}{0.449 - 0.013} \times 10.0$ μg./ml. $\times \frac{4}{1}$ = 23.0 μg./ml. "Corrected" U_1V_1 = 23.0 × 0.136 = 3.13 μg./min. The interpolated midpoint concentration in serum was 17.1 μg./ml. Hence C_{T-1824} = 0.183 ml. per min.

[7] In one of the subsequent studies, the control urine had a distinctly blue color. After centrifugation, most of the color was found concentrated in the sediment; microscopically, most of the dye could be seen in urinary tract epithelial cells, presumably in desquamated renal tubule epithelium. The dye slowly diffused from the cells on repeated extraction with physiological saline. Routinely, all urine specimens were centrifuged about one hour after the last clearance period preparatory to determining the dye concentration. It is assumed that the amount of dye diffusing from the cells of the sediment during the interval before centrifugation contributed about the same amount of dye (expressed as μg. per minute) to the control urine (U_0) as to subsequent urines; the resulting errors would, therefore, approximately cancel. In several other observations, the amount of dye concentrated in the sediment was much less than in the one described.

[8] Generous quantities of this albumin were obtained from the Department of Physical Chemistry, Harvard University, through the courtesy of Dr. David Gitlin.

TABLE I

Summary of data

Patient (hospital number)	Sex	Age	Duration of illness	Height	Ideal weight	Ideal surface area	Date	Observed weight*	ACTH therapy		Time of observation in relation to ACTH administration
									Duration	Dose	
(1)	(2)	*years* (3)	*months* (4)	*cm.* (5)	*Kg.* (6)	M^2 (7)	(8)	*Kg.* (9)	*days* (10)	*mg./24 hrs.* (11)	(12)
P. M. (580366)	M	3	7	95.0	14.7	0.60	11-1-50	17.2			1 day before
							11-7-50	17.6	8	50	7th day of ACTH
							11-13-50	15.3			5 days after
J. H. (576554)	M	4½	20	95.3	14.8	0.61	11-10-50	20.4			1 day before
							11-17-50	21.1	10	100	7th day of ACTH
							11-27-50	22.1			7 days after
E. B. (586965)	F	4½	4	106.0	17.7	0.69	12-6-50	21.7			10 days before
							12-15-50	21.5			1 day before**
							12-19-50	18.1	4	50	4th day of ACTH
M. B. (588663)	F	1¾	2	81.5	10.9	0.48	1-5-51	12.5			3 days before
							1-17-51	11.9	10	50	10th day of ACTH
W. H. (581715)	F	2½	11	77.0	9.8	0.44	2-7-51	18.1			3 days before
							2-13-51	10.7	10	50	10th day of ACTH
							2-20-51	7.9			7 days after
							2-26-51	8.2			13 days after
P. S. (574414)	M	2½	9	88.0	12.9	0.55	2-8-51	16.7			6 days before
							2-12-51	16.9			2 days before
							2-19-51	17.1	6	50	6th day of ACTH
H. G. (590159)	F	2	6	87.0	12.5	0.53	2-9-51	13.7			1 day before
							2-14-51	14.2	10	50	6th day of ACTH
							2-21-51	12.1			3 days after
							2-27-51	12.4			9 days after
B. L. (588864)	F	3¾	7	101.5	16.4	0.65	3-16-51	21.6			3 days before
							3-21-51	22.8	10	50	3rd day of ACTH
							4-5-51	20.0			8 days after
D. E. (604205)	M	4¼	9	101.0	16.3	0.65	7-11-51	20.6			2 days before
							7-20-51	14.2	5	50	3 days after
C. S. (597510)	M	3¼	15	100.0	16.2	0.64	6-3-52	28.3			2 days before
							6-18-52	24.0	10	75-100§§	4 days after
F. deK. (576121)	M	7½	38	114.0	20.7	0.79	3-20-51	21.1			4 days before
							3-30-51	22.3	10	50	7th day of ACTH
							4-9-51	23.0			7 days after

* In some cases, further weight loss ensued after the time of the last observation.
** Upper respiratory infection occurred between first and second observations.
§§ 75 mg. per 24 hrs. for four days, then 100 mg. per 24 hrs. for next six days.

sulted in large percentage errors in measuring the concentrations of both substances. Therefore, although the clearance ratio deviated from 1.0 to a considerable extent in some instances, the order of magnitude of C_{ALB} was estimated sufficiently well by C_{T-1824} for the purposes of the present investigation.

Total protein excretion

The decrease in total protein excretion during and after ACTH therapy was large in all cases, being roughly parallel to the decrease in C_{T-1824}/C_{IN} (Tables I and II). The ratio, total protein excretion/C_{IN}, provides a minimum estimate of the concentration of protein in the glomerular fluid (assuming no protein is secreted into the urine by the tubules). This ratio likewise decreased markedly.

Plasma and whole blood volume

Observations that the plasma volume usually increases after ACTH treatment (8) were not sus-

TABLE I—*Continued*

Summary of data

Plasma volume	Blood volume	C_{IN}†		C_{CR}/C_{IN}†	C_{PAH}†	$C_{T\text{-}1824}$‡	$\frac{C_{T\text{-}1824}}{C_{CR}}$‡	Estimated§ $\frac{C_{T\text{-}1824}}{C_{IN}}$	Total protein excretion‖	Estimated total protein excretion¶ $\frac{}{C_{IN}}$
ml. (13)	*ml.* (14)	*ml./min.* (15)	*Per cent of normal* (16)	(17)	*ml./min.* (18)	*ml./min.* (19)	*ml./100 ml.* (20)	*ml./100 ml.* (21)	*mg./min.* (22)	*mg./100 ml.* (23)
735	1,265	19.7	47	2.65	145	0.205	0.47	1.3		
730	1,110	25.2	60	1.77	113	0.054	0.13	0.22		
725	1,115	53.0	126	1.30	200	0.002	0.003	0.004		
765	1,020	6.3	15	1.60						
680	1,165	7.1	17	1.53	39.1	0.176	1.7	2.7		
690	1,080	10.9	26	1.42	29.3	0.080	0.47	0.67		
645	1,045	36.0	75	1.99	312	0.185	0.27	0.53		
720	1,205					0.054	0.11			
795	1,185	57.9	121	1.28	271	0.005	0.007	0.009		
420	725					0.054	0.12			
470	725					0.002	0.004			
555	725	8.8	29	1.59	37.2	0.183	1.4	2.2	4.5	54.0
420	665	8.0	26	1.30	37.9	0.035	0.33	0.43	0.6	6.7
440	670	11.7	38	2.23	52.7	0.024	0.078	0.17	0.4	2.9
445	640	22.4	73	1.07	82.4	0.085	0.29	0.31	2.4	10.4
660	1,040	51.0	134	1.48	136	0.153	0.20	0.29	2.4	4.8
750	1,210	47.4	125	1.27	173	0.049	0.10	0.13	1.9	4.1
845	1,325	56.2	148	1.45	156	0.010	0.012	0.017	0.2	0.4
		35.0	95	1.04	143	0.071	0.25	0.26	2.3	6.6
490	855	43.8	118	1.16	186	0.026	0.066	0.077	1.0	2.0
480	890	29.7	80	1.62	149	0.095	0.21	0.34	1.3	4.7
500	825	38.6	104	0.88	137	0.004	0.015	0.013	0.0	0.0
720	1,100	18.1††	40	2.81		0.58	1.05	2.95	3.0	13.8
635	1,050					0.47	1.27		1.8	
		41.9‡‡	93	1.52		0.19	0.27	0.43	1.8	4.4
715	1,070	26.9	60	1.68	156	0.124	0.28	0.47	1.8	6.7
720	1,070	55.2	122	1.20	228	0.002	0.003	0.003		
1,065	1,390	21.4	48	1.51	194	0.82	2.52	3.80	7.2	40.9
		25.3	56	1.35	145	0.084	0.22	0.30	1.8	6.5
1,160	2,000	21.9	40	1.47	64.6	0.016	0.047	0.069	1.3	5.6
1,085	1,870	25.5	46	1.36	76.5	0.005	0.015	0.021	0.2	0.7
985	1,690	23.2	42	1.67	76.2	0.001	0.004	0.006	0.2	1.0

† Data from periods U_{2-4}.
‡ Data from period U_1.
§ Calculated by multiplying the value for $C_{T\text{-}1824}/C_{CR}$, shown in column 20, by the value for mean C_{CR}/C_{IN}, measured in periods U_{2-4} and shown in column 17.
‖ Data from control period preceding period U_1.
¶ Calculated by dividing the value in column 22 by the estimated C_{IN}. The latter was estimated by dividing the observed C_{CR} by the value for mean C_{CR}/C_{IN} shown in column 17.
†† Datum from study of 3-13-51.
‡‡ Datum from study of 4-6-51.

tained by the present data (Table I). More often than not, the plasma volume did not increase significantly.

DISCUSSION

Hypotheses concerning the mechanism of proteinuria in children with the nephrotic syndrome were recently discussed by Chinard, Lauson, Eder, Greif, and Hiller, (1) and reviewed by Smith (28) and by Barnett, Forman, and Lauson (2). It has been shown (1) that following administration of concentrated human plasma albumin the calculated minimum concentrations of protein in the glomerular fluid commonly exceeded 100 mg. per

TABLE II

Simultaneous clearances of albumin and T-1824

Patient (hospital number)	Sex	Age	Date	Number of periods	C_{IN}	Plasma albumin concentration	Albumin clearance	T-1824 clearance	$\frac{C_{T\text{-}1824}}{C_{ALB}}$	$\frac{C_{T\text{-}1824}}{C_{IN}}$	Total protein excretion	$\frac{\text{Total protein excretion}}{C_{IN}}$	Comment
		years			*ml./min.*	*Gm./100 ml.*	*ml./min.*	*ml./min.*		*ml./100 ml.*	*mg./min.*	*mg./100 ml.*	
R. K. (548337)	F	4¾	5–25–51	2	10.2*	0.36	0.834	0.411	0.50	4.0*	5.5	64.4*	(Severe edema)
D. E.† (604205)	M	4¼	7–11–51	1	26.3*	0.48	0.205	0.124	0.61	0.47*	1.8	6.7*	Before ACTH
			7–20–51	1	63.9*	1.51	0.0010	0.0019	1.81‡	0.003*			After course of ACTH
L. A. (619414)	M	2¾	1–28–52	1	19.1*	0.74	0.397	0.291	0.73	1.5*	3.5	20.4*	Before albumin (moderate edema)
			1–28–52	3	22.8	2.16	0.524	0.525	1.00	2.3	10.6	46.1	One hr. after 12.5 Gm. of albumin intravenously
C. S.† (597510)	M	3¼	6–3–52	1	21.6*	0.37	1.59	0.821	0.52	3.8*	8.2	38.0*	Before albumin
			6–3–52	2	21.4	1.17	1.43	1.55	1.08	7.3	34.6	110.6	One hr. after 12.5 Gm. of albumin intravenously. Temp. 39.6° C.
			6–18–52	4	25.3	0.64	0.157	0.077	0.49‡	0.30	1.8	6.5	After course of ACTH

* C_{IN} estimated from observed C_{CR} and the C_{CR}/C_{IN} ratio measured in subsequent periods.
† See Table I for other data on this patient.
‡ The low concentrations of albumin and T-1824 in these urines exaggerate the analytical errors.

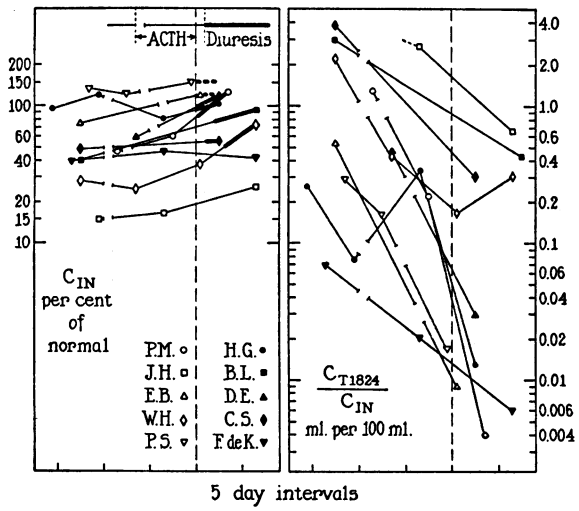

FIG. 1. CHANGES IN INULIN CLEARANCE (C_{IN}) (LEFT) AND IN THE RATIO OF T-1824 AND INULIN CLEARANCES (C_{T-1824}/C_{IN}) (RIGHT) RESULTING FROM ADMINISTRATION OF CORTICOTROPIN (ACTH) IN CHILDREN WITH THE NEPHROTIC SYNDROME

See Text for method of estimating C_{T-1824}/C_{IN}. The break in the lines connecting the symbols indicates the first day of ACTH treatment. The interrupted vertical line in each graph indicates the end of the last day of ACTH administration. The thickened section of the lines connecting the symbols (left) indicates the presence and duration of diuresis.

100 ml.; values as high as 193 mg. per 100 ml. were observed. These data, therefore, were not compatible with the view that proteinuria in children with the nephrotic syndrome results from a failure of the renal tubules to absorb the 20 or 30 mg. of protein commonly assumed to pass through normal glomerular walls with each 100 ml. of filtrate. For this and other reasons, it was concluded that proteinuria in the nephrotic syndrome was due to an increase in the glomerular permeability to proteins, especially to albumin (1).

In the control studies on three patients of the present report (W. H. and C. S., Table I, and R. K., Table II) minimum concentrations of protein in glomerular fluid were 54, 41, and 64 mg. per 100 ml., respectively. After infusion of concentrated albumin, values of 46 and 111 mg. per 100 ml., respectively, were obtained in patients L. A. and C. S. (Table II). All of these concentrations exceed the assumed normal values of 20 to 30 mg. per 100 ml. These results, therefore, are in agreement with those of Chinard, Lauson, Eder, Greif, and Hiller (1).

To the extent that the ratio, C_{T-1824}/C_{IN}, estimates the ratio, C_{ALB}/C_{IN}, and to the extent that the latter provides a rough indication of the minimum permeability of the glomerular walls to albumin, relative to the permeability to water, the data of the present investigation clearly indicate that treatment with ACTH (and presumably also with Cortisone) results in a marked degree of reversal of the functional pathology in the glomeruli. The usual increase in GFR may be considered another aspect of this same restorative process. As discussed in detail elsewhere (2), it is our present opinion that these effects on the glomeruli are primary and that most of the other beneficial effects of the treatment are secondary.

SUMMARY

Simultaneous renal clearances of the blue dye, T-1824 (C_{T-1824}), and of albumin (C_{ALB}) have been shown to be nearly the same in patients with the nephrotic syndrome (4). Furthermore, the ratio of the clearances of albumin and inulin (C_{ALB}/C_{IN}) provides a rough indication of the minimum glomerular permeability to albumin, relative to the permeability to water.

In 10 edematous children with the nephrotic syndrome the ratio, C_{T-1824}/C_{IN}, ranged from 0.26 to 3.8 ml. per 100 ml. before treatment with corticotropin (ACTH). Glomerular filtration rate (GFR), as estimated by C_{IN}, ranged from 15 to 134 per cent of average normal. From 50 to 100 mg. of ACTH per day were given intramuscularly in divided dosage every six hours for from four to ten days. By the end of, or a few days after, the course of injections, C_{T-1824}/C_{IN} had decreased strikingly in all patients: more than 10-fold in all but two. C_{IN} increased at least slightly in most cases and more than doubled in four. Similar results were observed in one non-edematous boy with chronic glomerular nephritis who excreted only 1 to 2 grams of protein per day. In the control study, C_{T-1824}/C_{IN} was only 0.07 ml. per 100 ml.; after ACTH it had decreased to 0.006 ml. per 100 ml.

The data of this investigation are interpreted as indicating that one of the favorable effects of ACTH treatment is a reversal toward normal of

the increased glomerular permeability to albumin (and other plasma proteins). The same restorative process is presumably responsible for some of the observed increase in GFR. These effects of therapy on the glomeruli are considered to be primary to most of the other beneficial results.

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