Corticoid Excretion during Diuresis in Nephrosis

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In 1953 Farnsworth [5], Galán et al. [6], McCall and Singer [10] estimated the corticoid excretion in the urine of nephrotic patients; in untreated subjects they found normal amounts. When their results were evaluated with regard to the therapeutic effect of adrenocorticotrophic hormone, i. e. with regard to the subsequent diuresis, it turned out that the higher corticoid excretion had risen during treatment the more likely was the success of treatment, in other words, that diuresis will result and the oedema disappear. The above-mentioned authors carried out their estimations chiefly during ACTH treatment and did not follow the changes in corticoid excretion during diuresis.

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In former investigations we found corticoid excretion in untreated nephrotic children to be considerably below normal [4]. In the present investigations we studied corticoid excretion during hormonal treatment and diuresis.

Daily corticoid estimations were made in the urines of five nephrotic patients during 8 courses of treatment with ACTH or steroid. In one of the patients (D. I.) were only found symptoms indicative of reduced glomerular filtration rate. Determination of reducing corticoids was carried out in 24 hour urine samples according to Heard, Sobel and Venning [7]. In each case the whole 24 hour urine specimen was studied and, in addition to the fraction hydrolyzed by acid, the corticoids excreted in glucuronide form were also estimated. For the latter procedure calf-spleen-glucuronidase prepared by ourselves was used [3].

ACTH as well as steroid treatment will raise the amount of corticoids excreted in the urine: the former by enhancing the endogenous hormone-production, and the latter by discharging the waste products of the administered steroid. Therefore it was first studied to what extent corticoid excretion is influenced by hormone treatment.

I. ACTH Treatment

ACTH (Cortrophine-Z, Organon) treatment was applied altogether three times. During treatment there

TABLE I

Patient	Treatment (days)	Corticoid in mg per 24 hours		
		Acid hydrolyzable	Glucuronide	Total
D. I.	— (3 days)	*0.34* (0.20—0.48)	*0.45* (0.30—0.56)	*0.79* (0.50—1.79)
	Zn-ACTH (5 days)	*0.83* (0.42—1.30)	*0.54* (0.29—0.62)	*1.37* (0.71—1.92)
K. Á.	— (3 days)	*0.38* (0.34—0.40)	*0.25* (0.23—0.27)	*0.63* (0.61—0.64)
	Zn-ACTH (4 days)	*1.86* (0.41—3.82)	*1.12* (0.22—2.16)	*2.98* (0.34—8.98)
K. Á.	— (4 days)	*0.16* (0.04—0.48)	*0.15* (0.06—0.25)	*0.31* (0.16—0.73)
	Zn-ACTH (8 days)	*0.50* (0.07—1.28)	*0.45* (0.08—1.02)	*0.95* (0.19—2.28)

occurred a 3 to 5 fold increase in the excretion of corticoids hydrolyzable with acid. The amount of corticoids excreted as glucuronides increased in a similar way in two cases. In the third case (D. I.) no change could be observed. In this patient a glomerular filtration was reduced (endogenous creatinine clearance was 38 ml/min per 1.73 sq. m surface area). The results of ACTH treatment are given in Table I.

The sometimes tenfold difference in the extreme values during ACTH treatment was due to the fact that during treatment corticoid excretion gradually rose from the low initial values to their tenfold.

II. Steroid Treatment

The effect of treatment with prednisone (Di-Adreson, Organon, Oss) and that of prednisolone (Prednisolon, Chinoin, Budapest) on corticoid excretion were examined altogether four times, in three patients. In Table II it may be seen that during steroid administration corticoid excretion showed an about fourfold increase. This increase was marked first in the acid hydrolyzable fraction and then in the glucuronide fraction; total excretion was invariably increased.

III. Diuresis

Whether diuresis was produced by ACTH or steroid treatment, the excretion of both corticoid fractions continued to increase. As seen in Table III, during diuresis the 24 hour urine specimen contained 2 to 5 times more corticoids than during the previous period of hormone treatment.

In Table III the upper figures in italics represent the average values during treatment. Below these figures the extreme values can be seen in brackets. E. g., in the case of patient

TABLE II

Patient	Treatment (days)	Corticoid in mg per 24 hours		
		Acid hydrolyzable	Glucuronide	Total
O. I.	— (5 days)	*0.23* (0.15—0.30)	*0.23* (0.09—0.48)	*0.46* (0.25—0.78)
	Prednisone (10 days)	*0.86* (0.32—1.88)	*1.09* (0.18—2.20)	*1.96* (0.60—3.60)
P. J.	— (1 day)	*0.60*	*1.27*	*1.87*
	Prednisone (7 days)	*3.38* (1.14—4.72)	*3.89* (1.49—7.07)	*7.27* (2.63—11.52)
P. J.	— (1 day)	*0.53*	*0.18*	*0.71*
	Prednisolone (4 days)	*0.85* (0.60—1.18)	*1.97* (0.73—4.00)	*2.82* (1.91—4.80)
Sz. I.	— (3 days)	*0.50* (0.16—1.00)	*0.30* (0.09—0.56)	*0.80* (0.25—1.56)
	Prednisolone (6 days)	*1.09* (0.50—1.57)	*0.43* (0.26—0.59)	*1.52* (0.76—2.07)

K. Á., total corticoid excretion during ACTH treatment averaged 2.99 mg/day, with the extreme values 0.35 mg and 5.98 mg. The lower figures in italics indicate the average values during diuresis, again with their extremes. Thus, during diuresis the excretion of total corticoids averaged 11.70 mg/day with the extreme values 8.12 mg and 20.00 mg. In this Table the values of corticoid excretion before treatment have not been indicated; they can be seen in Tables I and II. The corticoid fractions hydrolyzable by acid and glucuronidase, respectively, showed an increase of about the same degree.

In one case (P. J., Table III, Case 5) it was possible to follow the changes in corticoid excretion during spontaneous diuresis. The amount of both corticoid fractions was increased about twofold; after diuresis the values returned to the original level.

Comparing the changes in the amount of urine during ACTH or steroid-induced diuresis with those observed during spontaneous diuresis it was remarkable that during spontaneous diuresis the amount of urine and that of corticoid excretion increased in parallel. During diuresis following hormone treatment, however, the increase in corticoid excretion was nearly twice as high as the increase in urine output.

DISCUSSION

Although the diuretic effectiveness of adrenocortical hormones in nephro-

TABLE III

Patient (Treatment)	Period (days)	Corticoid in mg per 24 hours		
		Acid hydrolyzable	Glucuronide	Total
K. Á. (ACTH)	Before diuresis (4 days)	*1.86* (0.41—3.82)	*1.13* (0.22—2.16)	*2.99* (0.34—5.98)
	During diuresis (5 days)	*9.45* (7.20—15.50)	*2.31* (0.92—4.50)	*11.76* (8.12—20.00)
K. Á. (ACTH)	Before diuresis (8 days)	*0.50* (0.07—1.28)	*0.45* (0.08—1.02)	*0.95* (0.19—2.28)
	During diuresis (3 days)	*1.48* (1.30—1.78)	*1.56* (0.70—3.14)	*3.04* (2.07—2.13)
P. J. (Prednisone)	Before diuresis (7 days)	*3.38* (1.14—4.72)	*3.89* (1.49—7.07)	*7.27* (2.63—11.52)
	During diuresis (4 days)	*8.28* (5.69—16.26)	*7.56* (4.70—11.23)	*13.34* (7.56—20.96)
P. J. (Prednisolone)	Before diuresis (4 days)	*0.85* (0.60—1.18)	*1.97* (0.73—4.00)	*2.82* (1.91—4.80)
	During diuresis (3 days)	*3.45* (2.32—4.02)	—	—
P. J. (Spontaneous diuresis)	Before diuresis (5 days)	*0.30* (0.14—0.48)	*0.43* (0.15—0.68)	*0.73* (0.37—0.98)
	During diuresis (4 days)	*0.58* (0.42—0.88)	*1.06* (0.34—1.48)	*1.64* (0.86—2.14)
	After diuresis (5 days)	0.37 (0,16—0,54)	*0.34* (0.17—0.58)	*0.71* (0.44—1.06)
Sz. I. (Prednisolone)	Before diuresis (6 days)	*1.09* (0.50—1.57)	*0.43* (0.26—0.59)	*1.52* (0.76—2.07)
	During diuresis (1 day)	*2.00*	*1.70*	*3.70*

sis has been known for almost a decade, the mechanism of the effect has not been clarified [1]. The general opinion is that the increased volume of circulating blood plays an important role. Some authors ascribe a decisive effect to the improvement of glomerular filtration which may or may not be due to the increased volume of circulating plasma [2]. This assumption is supported by the experience that diuresis appears on the 8th to 12th day of hormone treatment, by which time under the effect of the hormone an increase has occurred in the volume of circulating plasma. This, however, is not the only possibility and does not explain uncondi-

tionally the sudden onset of diuresis. Some swift mechanism becoming operative under certain circumstances may play a role here: it may be the aldosterone activity which decreases with the increasing volume of circulating plasma [8], or a drop in the antidiuretic hormone level of the posterior pituitary gland [9]. The decrease in vascular permeability resulting from blockage of a possible antigen-antibody reaction may also be of importance [9]. Although all these changes can be demonstrated clearly, they are interpreted differently.

There is no doubt about the important part of the adrenal hormones in creating conditions suitable for the onset of diuresis. The question now is, whether the increase in corticoid excretion during diuresis observed by other authors as well as by ourselves speaks for an active role of the adrenals, or represents merely a result of changed renal function?

The steroid doses used in the treatment of nephrosis (60 to 80 mg prednisteroid or 200 to 300 mg cortisone daily) are sufficient to reduce, through inhibition of pituitary ACTH secretion, the secretory activity of the adrenals to a very low level, one corresponding to that after hypophysectomy. Under such circumstances it may hardly be expected that, in spite of the supernormal corticoid level in the serum, ACTH mobilization should result and the adrenal glands produce a multiple of the usual hormone output during diuresis.

It is similarly unlikely that the adrenals having been forced to maximal performance by ACTH administration should increase their hormone production.

Therefore the assumption seems more probable that the increased amount of steroid excreted during diuresis originates from the removed oedema fluid.

Thus it is believed that the increased corticoid excretion during diuresis is not due to an increased secretory activity of the adrenals, but to changes in renal haemodynamics and tubular function. In other words, it is in no relationship with the factors enhancing the urine output but with those associating themselves with diuresis.

Summary

The changes inexcretion of reducing corticoids in the urine of nephrotic patients during diuresis induced by ACTH or steroid treatment have been studied. The corticoid excretion elevated by the hormone treatment was further raised during diuresis. It is suggested that this rise reflects renal rather than adrenal activity.

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