Electrolyte and Water Responses of Normal Subjects During Cortisone Administration.* (20494)

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During studies in which cortisone acetate was administered to healthy young subjects, estimations of Evans blue space, thiocyanate space, serum electrolyte concentration and urine electrolyte excretion were made. Such information, generally not available from studies of normal subjects, is here reported.

Methods. Five ambulatory male medical students ranging in age from 22-26 years were studied during the intramuscular administration of cortisone acetate in doses of 50 mg 4 times per day for periods of 3 to 5 days. One subject was also observed while receiving cortisone acetate orally in doses of 50 mg 4 times per day for 4 days.

The meals of each subject were supervised by a medical dietitian† who selected a fixed diet resembling that ordinarily consumed by the individual. The caloric content of these diets ranged from 2400-3200 calories. The intake of sodium chloride was fixed at the usual daily level for each subject and ranged from 9-12 g daily. Water was consumed *ad libitum.*

Experiments were divided into 3 periods: Pretreatment, 4 or more days; treatment, 3 to 5 days; and post-treatment, 5 or more days.

All observations were made daily while the subjects were fasting and recumbent.

Blood in double oxalate(1) collected daily at 8:00 A.M. was used for the following determinations in duplicate: Hematocrit (3,000 r.p.m. for 30 minutes); red blood cell count, using 2 certified pipettes (an average of 4 counts, 2 from each pipette); and hemoglobin by the alkaline hematin method using the Evelyn macrocolorimeter(2). Serum was analyzed for sodium and potassium using a flame photometer with an internal lithium standard(3) and for chloride(4).

The freezing point depression(5,6) was determined by means of an electrical resistance thermometer (Western Electric Co., Thermistor No. 14A). The reproducibility of this method is demonstrated by the fact that 15 determinations on a standard glucose solution, each performed on different days, showed a mean freezing point of —0.520°C with a standard error of ±0.001°C.

A daily 24-hour urine collection was analyzed for sodium(3), potassium(3), and chloride(4).

Evans blue space was determined by a modification(7) of the method of Gibson and Evans(8) using specimens of serum from venous blood collected at 15, 30, 45, and 60 minutes after the injection of 10 ml of a 0.1% solution of the dye. Thiocyanate space was determined by a modification(7) of the method of Crandall and Anderson(9) using serum from blood collected at one, 2, and 3 hours after the intravenous injection of 8 ml of a 10% solution of thiocyanate. Thiocyanate space was not corrected for binding by albumin(10) since the correction for albumin in extra-vascular fluid is not feasible(11).

Result. A. *Blood and serum studies.* (Table I). (Values in Table I are averages of individual means which were computed for each subject by period.) Erythrocyte, hemoglobin, and hematocrit values decreased slightly during drug administration, and after treatment they approached but did not reach pretreatment figures. Serum electrolyte concentration and freezing point depression were unaltered during drug administration and in the post-treatment period.

* Supported in part by grants from the National Heart Institute (Research Grant H-177-C2) and from the Lederle Laboratories Division, American Cyanamid Co.

† We are indebted to Dr. George W. Thorn for this service.

TABLE I. Mean Erythrocyte, Hemoglobin, Hematocrit, Serum Electrolyte and Serum Freezing Point during Experiments with Cortisone Acetate. Mean ± standard deviation of sample.

	Pre-treatment period	Treatment period	Post-treatment period
R.B.C., cells/mm³	4.95 ± .56*	4.47 ± .46	4.62 ± .20
Hgb, g/100 cc	15.1 ± 1.5 * (14.8) †	14.2 ± 1.5 (13.2) †	14.4 ± 1.0 (13.4) †
Hematocrit, %	47.5 ± 4.7 * (43)	42.5 ± 2.6 (39)	43.2 ± 2.9 (41)
Serum Na^+, mEq/L	142.2 ± 3.4 * (142)	139.6 ± 1.5 (145)	139.0 ± 3.4 (148)
Serum K^+, mEq/L	4.2 ± .6 * (4.2)	4.0 ± .2 (3.9)	4.1 ± .2 (3.7)
Serum Cl^-, mEq/L	107.6 ± 1.14* (104.3)	107.2 ± 2.16 (105.5)	107.6 ± 1.14 (103.8)
Serum freezing point, °C	−.546 ± .008*	−.547 ± .013	−.546 ± .011

* Mean ± stand. dev. during intramuscular administration.
† Figures in parentheses are the values of subject 1 during oral administration.

TABLE II. Urine Volume and Electrolyte Excretion during Experiments with Intramuscular Cortisone Acetate.

	Subject	Pre-treatment period	Treatment period	Post-treatment period
Na^-, mEq/24 hr	1	155 (132)*	103 (109)*	201 (221)*
	2	150	153	194
	3	158	104	252
	4	130	90	212
	5	151	75	140
	Mean	149	105	200
K^-, mEq/24 hr	1	71 (81)	121 (82)	73 (90)
	2	102	94	75
	3	74	71	68
	4	89	96	68
	5	71	121	73
	Mean	86	90	71
Cl^-, mEq/24 hr	1	140 (147)	130 (133)	207 (221)
	2	188	170	180
	3	216	158	230
	4	124	110	227
	5	167	107	160
	Mean	167	137	201
Vol, cc/24 hr	1	957 (975)	1109 (1046)	1180 (1482)
	2	988	1042	976
	3	1673	1548	2042
	4	827	984	1730
	5	2148	2230	2454
	Mean	1319	1383	1676

* This subject was also observed after cortisone acetate orally, the results of which are tabulated in parentheses for comparison purposes only. They are not included in the means.
Values are means of pooled data for each individual by period.

B. *Urine volume and electrolyte studies.* (Table II) (Values are means of pooled data for each individual by period.) Sodium excretion was reduced during cortisone acetate administration in 4 or 5 individuals, and was increased in the post-treatment period in all subjects. Chloride excretion was uniformly reduced during treatment and increased after drug administration. Potassium excretion increased in 2 of the 5 individuals during cortisone acetate administration. Urine volumes were unaffected by cortisone administration,

TABLE III. Evans Blue Space, Thiocyanate Space and Body Weight during Intramuscular Administration of Cortisone Acetate.

	Subject	Pre-treatment* period	Treatment† period	Post-treatment‡ period
Evans blue space, cc	1	2730 (3330) §	3240 (3530) §	3310
	2	2970	3890	3240
	3	2330	3150	
	4	3860	3520	3520
	5	3520	3680	3930
	Mean	3082	3496	3500
Thiocyanate space, cc	1	15530 (16250)	18270 (17430)	18560
	2	17200	18770	17920
	3	14650	18700	
	4	18320	21590	18790
	5	18270	19580	20600
	Mean	16794	19382	18968
Body wt, kg	1	71.6 (70.2)	73.5 (71.6)	73.7
	2	81.6	82.0	81.6
	3	73.7	73.5	
	4	70.5	72.6	69.5
	5	67.5	68.4	69.3
	Mean	73.0	74.0	73.5

* Determined just before cortisone administration begun.
† " " " last dose of cortisone.
‡ " 2-5 days after therapy was terminated.
§ This subject was also observed after cortisone acetate orally, the results of which are tabulated in parentheses for comparison purposes only. They are not included in the means.

although in 3 individuals there was an elevation in the post-treatment period. Since water was ingested *ad libitum* the meaning of the urine volume changes is uncertain.

C. *Evans blue space, thiocyanate space, and body weight.* (Table III). (Individual values are shown.) Evans blue space increased in 4 of 5 instances during the intramuscular administration of cortisone acetate and in the subject receiving cortisone orally. (Pretreatment values on this same subject performed twice under identical conditions of diet and salt intake, however, differed by 600 cc). Post-treatment figures revealed no consistent pattern. Thiocyanate space increased in every instance during drug administration including the one experiment with oral administration. The post-treatment response was not consistent. Small increases in body weight were noted to drug administration in all experiments except in subject No. 3 whose weight dropped 0.2 kg. The post-treatment response varied.

Discussion and conclusions. The data indicate that normal subjects given cortisone acetate respond in a similar manner to that observed in patients: salt and water retention occurs and serum electrolyte concentration and serum osmolarity are not appreciably altered(12-14). The responses noted here in Evans blue space are similar to the variable results seen in subjects with disease during cortisone administration(15-19). The uniform increase in thiocyanate space is not an unexpected finding since evidence of chloride retention was uniformly noted and since the thiocyanate space empirically parallels changes in chloride space(20-21). The weight gain noted by most of the subjects was considered to represent changes in total body water since the diets, including salt intake, were at the usual daily level for all subjects and the experiments were of brief duration. These data do not make it possible to separate salt and water retention from endogenous shifts of cell water to extracellular space.

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Received July 9, 1953. P.S.E.B.M., 1953, v83.

Effect of Stress upon the Healing of Wounds in Rats.* (20495)

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Although the phenomena related to stress have been intensively studied in the past few years, the effect of stress upon the healing process has never been clearly determined. Stress results in increased secretion of adrenal cortical hormones(1). The administration of ACTH or cortisone, in sufficient dosage, inhibits the rate of healing(2,3). Whether or not the increased endogenous secretory activity of the pituitary-adrenal axis in response to stress can depress the rate of healing of an experimental wound, is not established.

Studies concerning the effect of stress upon healing have led to contradictory conclusions. It has been reported(4,5) that if 2 wounds are produced in an animal at different times, the second wound heals more rapidly than the first. On the other hand, it has also been reported(6) that a skin defect, made one or 2 days following a procedure such as gonadectomy, healed more slowly than similar wounds made some time after the operative intervention. Intercurrent infections, located some distance from healing wounds, were observed to slow the rate of healing in a few animals (7). Intramuscular injections of an irritant, sodium ricinoleate, reportedly reduced the rate of healing in dogs on the 7th and 10th postoperative days(8).

In an attempt to clarify the relationship between pituitary-adrenal function and the healing process, a series of experiments was begun in this laboratory in 1951 utilizing the bursting pressure of standard laparotomy

* Supported by a grant under contract with the Medical Research and Development Board, Department of the Army. (Contract No. DA-49-007-MD-162).