sibly of LTH, could be viewed in terms of improvement in the general physiologic state of the organism. It would appear, however, that LTH and STH act by different mechanisms, since the former, but not the latter, consistently produces an increase in the proportion of glandular tissue in the ventral prostate.

Summary and conclusions. Lactogenic hormone (LTH) alone or together with testosterone propionate (TP) produced a significant increment in the weight of the seminal vesicle. When given with TP, LTH produced an increase in the amount of glandular tissue in the ventral prostate. Growth hormone (STH) alone or together with TP did not produce any consistently significant increase in the weight of the accessories. When TP, LTH and STH were administered simultaneously to the same test animals, the weight response of all accessories was significantly greater than that to androgen alone. The data are interpreted as indicating that a synergism among the 3 hormones may operate to stimulate sex accessory growth in the male Sprague-Dawley rat.

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Received January 8, 1957. P.S.E.B.M., 1957, v94.

Effects of Cortisone and Hydrocortisone on Sodium Excretion in Adrenalectomized Rats. (23051)

C. M. KAGAWA AND C. G. VAN ARMAN

Division of Biological Research, G. D. Searle and Co., Chicago, Ill.

Sodium retention with cortisone and hydrocortisone is readily demonstrated in man (1-4). In adrenalectomized rats, commonly used for steroid studies, retention of sodium has not been clearly seen. Singer and Venning(5) in fact observed sodium loss with cortisone, but were unable to obtain a graded response. Results of Johnson(6) and of Dorfman(7) showed increased excretion of the ion with small doses of hydrocortisone, and no effect with larger doses. In our experience, cortisone has caused a loss of sodium with low doses and retention with high doses. It should be carefully noted that a fixed time-interval of urine collection was used for all the foregoing laboratory studies.

Sodium response in rats was therefore further investigated as a function of time and dose following cortisone and hydrocortisone administration. Information of this kind is useful for careful evaluation of sodium-retaining activity in structurally-related steroids. The present report summarizes our data.

Material and methods. Exp. I. Large

TABLE I. Effects of Large Doses of Cortisone and Hydrocortisone on Sodium Excretion in Consecutive Samples of Urine.

Treatment†	mg/rat	No. of animals	μEq sodium/105 min. period (mean ± S.E.) 1st	2nd	3rd	4th
CO		26	96 ± 10	63 ± 5	41 ± 4	30 ± 3
E	.5	12	86 ± 14	81 ± 16	92 ± 13*	98 ± 15
	1.0	12	91 ± 11	61 ± 6	105 ± 11*	125 ± 12*
F	.5	10	79 ± 7	46 ± 8	64 ± 7*	92 ± 10*
	1.0	10	80 ± 8	37 ± 5*	56 ± 7	86 ± 12*

* P = .05 or less. † CO = Corn oil; E = Cortisone; F = Hydrocortisone.

doses of cortisone and hydrocortisone were given to adrenalectomized rats, and the effects on sodium excretion determined in consecutive samples of urine. This study provided data on time-response relationships with the steroids. Sprague-Dawley male rats (140 to 175 g) adapted to laboratory conditions for about a week were starved overnight. Animals were tube-fed with 10 ml of a suspension containing 3.8 g rat food (Rockland Farm) at 9 a. m. and 4 p. m. for 2 consecutive days. Bilateral adrenalectomy was performed under ether anesthesia at 11 a. m. on the 2nd day of feeding. Tap water was provided *ad libitum* during the tube-feeding regime. Doses of 0.5 and 1 mg of steroids in 0.2 ml corn oil (Mazola) were subcutaneously injected on the morning of the 3rd day. Control rats received the same volume of oil. Each animal was forced to void by application of pressure to the bladder, and then placed in an individual metabolism cage. Following injection, 4 consecutive samples of urine were collected at intervals of 105 minutes. Complete specimens of urine were obtained at the end of each period by manipulation of the bladder and by rinsing cages with distilled water. Sodium concentration was determined with the Beckman flame photometer for calculation of total excretion per period. Relative differences in excretion between control and treated animals were computed for each period to examine the influence of the steroids. *Exp. II.* This study was to determine the influence of dose (0.0625 to 0.5 mg) of hydrocortisone upon time-response relationships. Detailed procedures were similar to those described for Exp. I.

Results. The effects of 0.5 and 1 mg cortisone and hydrocortisone on sodium excretion are summarized in Table I. Changes in sodium excretion compared with the control group are plotted in Fig. 1. In general, sodium retention preceded a diuretic phase with both 0.5 and 1 mg doses. Initial retention was small with cortisone (E), but by virtue of a strong diuresis during periods 3 and 4, sodium loss resulted for the total period of study. Both groups receiving hydrocortisone (F) responded initially with relatively greater retention of sodium and subsequently with increasing diuresis. The net effect with F is likewise sodium loss, but is less pronounced than that of E.

For both steroids, 1 mg seemed more effective than 0.5 mg in delaying onset of sodium diuresis. Inspection of curves indicates that there is more prolonged duration of sodium retention with increasing doses. This effect is exemplified by Fig. 1 which shows that length of retention phase varies directly as dose of E. A similar relationship between dose and duration of retention phase

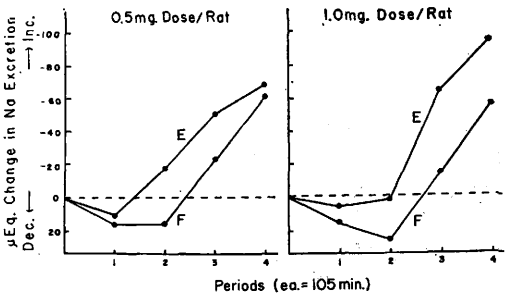

FIG. 1. Relative changes in excretion pattern of sodium following inj. of large doses of cortisone (E) and hydrocortisone (F). Values above control line (– – – – –) represent increased excretion and values below, retention.

TABLE II. Effects of Graded Doses of Hydrocortisone on Sodium Excretion in Consecutive Samples of Urine.

Treatment†	mg/rat	No. of animals	μEq sodium/105 min. period (mean ± S.E.) 1st	2nd	3rd	4th
CO		10	65 ± 8	50 ± 7	51 ± 9	43 ± 11
F	.0625	10	81 ± 7	66 ± 7	66 ± 9	69 ± 8
	.125	10	59 ± 7	65 ± 10	76 ± 8	89 ± 6*
	.25	10	58 ± 6	51 ± 7	82 ± 6*	100 ± 9*
	.5	9	56 ± 7	42 ± 7	80 ± 12	102 ± 12*

* P = .5 or less. † CO = Corn oil; F = Hydrocortisone.

is seen with curves of F, but the differences are not so marked.

Data concerning the temporal phase of sodium retention as a function of dose of F were obtained in Exp. II (Table II). The total time required for the excretion rate of sodium to equal that of the controls was estimated from the time-response curves. A value of zero was assigned to the group receiving 0.0625 mg F, since no retention of sodium occurred in any of the 4 periods of study. Curve I of Fig. 2 illustrates relationship between dose of steroid (log scale) and duration of sodium retention. Results with 0.5 and 1 mg F from the previous experiment are shown as Curve II in the Figure. This method of evaluation is only roughly quantitative, but it demonstrates the direct relation between duration of retention phase and dosage. Examination of data in the Table reveals, on the other hand, that degree of sodium retention appears relatively less dependent upon dose of these steroids.

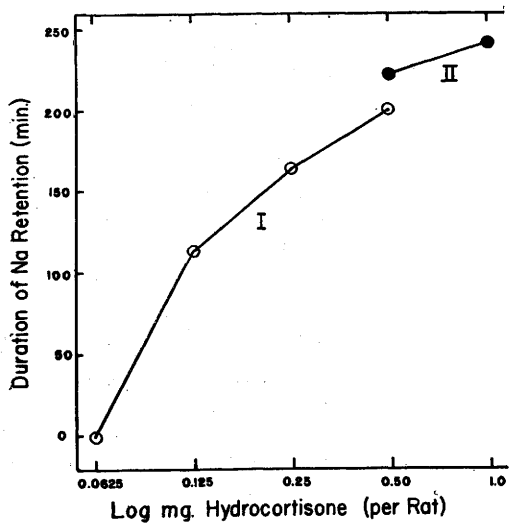

FIG. 2. Relationship between duration of sodium retention and dose of hydrocortisone (log scale). Curves I and II represent separate studies.

Discussion. Our results show that large doses of E and F cause a biphasic effect on sodium excretion. In general, a small retention precedes a strong diuresis, the net effect being sodium loss. Smaller doses hasten onset of secondary excretion phase and decrease duration of sodium retention. It is evident that entirely different results are possible by varying the time-interval of urine collection. Increased excretion will be the predominant phenomenon over a long period, because the sample includes a large segment of secondary diuretic phase. With a shorter collection period, no change will occur because retention is opposed by the same degree of sodium diuresis. Finally, only sodium retention will be found with relatively brief collection. A careful evaluation requires the testing of a wire range of doses to discover secondary effects which may be operating.

Our results indicate that E and F are capable of retaining sodium in adrenalectomized rats, as they do in man(1-4). However, degree of retention appears weak and only transient in comparison with the secondary excretion phase, and consequently is demonstrable only with large doses under special conditions of urine collection.

The biphasic nature of sodium excretion does not seem to be confined to the actions of E and F. An early report by Harrop(8) shows that α-estradiol caused an initial retention, then a loss of sodium in normal dogs maintained with constant fluid and mineral intake. Simpson and Tait(9) have discussed

a biphasic response with DCA, which elicited a net loss of sodium in adrenalectomized rats. The data of Forsyth(10) suggest the strong influence of this phenomenon with DCA, by showing increased excretion with small doses, and retention with larger doses in adrenalectomized mice.

Summary. 1. The influence of time and dosage upon sodium excretion by rats was investigated after cortisone and hydrocortisone administration. 2. Results of time-response studies show that large doses cause initially weak and transient retention of sodium and subsequently strong excretion of the ion. Smaller doses reduce progressively duration of retention phase and hasten onset of secondary diuresis. 3. Two factors appear to influence the response of sodium excretion. During a fixed time-interval of urine collection, increasing doses cause excretion, no change and retention of sodium. Similar changes in excretion of the ion are seen with a given dose when collection interval is progressively shortened.

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Received January 10, 1957. P.S.E.B.M., 1957, v94.

Comparison of Tissue and Plasma Thromboplastic Activities.* (23052)

JESSICA H. LEWIS AND PAUL DIDISHEIM†
Department of Medicine, University of Pittsburgh.

Since introduction of the thromboplastin generation test by Biggs and Douglas(1) a great many studies have been carried out dealing with defective formation of "plasma thromboplastin" in various coagulation abnormalities. This plasma thromboplastin is defined as activity developed in a dilute mixture of adsorbed plasma ($Al(OH)_3$ or $BaSO_4$), serum, platelets and calcium. When samples of such a mixture, together with additional calcium, are added to normal plasma "thromboplastic" activity develops during 5-minute incubation as clotting times decrease from over a minute to approximately 10 seconds. Relatively little attention has been paid to the activity of fully formed normal plasma thromboplastin in the clotting mechanism. A distinct difference between plasma and tissue thromboplastin was demonstrated by Gollub, Ulin and Black who showed that the bacterial enzyme thromboplastinase would inactivate tissue thromboplastins, but not plasma thromboplastin, although it did have some inhibitory effects in early stages of plasma thromboplastin generation.

The simple experiments presented in this study show certain striking differences between tissue and plasma thromboplastin.

Materials and methods. Tissue thromboplastin: Human Brain: 300 mg acetone-dried human brain powder suspended in 5

* Supported by research grants from N.I.H., U.S.P.H.S., and Pittsburgh Chapter of Hemophilia Foundation.

† Post-doctorate fellow, Life Insurance Medical Research Fund.