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Increase in Pulsatile Secretion of Growth Hormone during Failure of Catch-Up Growth following Glucocorticoid-Induced Growth Inhibition[1] (42031)

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Abstract. The pattern of growth hormone (GH) secretion was determined in rats injected with cortisone acetate, 5 mg/rat/day subcutaneously, or with an equivalent volume of saline for 4 days from age 40 days. Cortisone injections resulted in inhibition of growth of body weight and tail length. During recovery the rats resumed a normal rate of growth but failed to show catch-up growth acceleration. From 17 to 27 days of recovery, plasma was sampled at 15-min intervals through the lights-on period, 06:00 to 18:00, via a catheter chronically implanted in the superior vena cava. During sampling each rat was housed singly in an insulated chamber, unrestrained, and with food and water *ad lib.* Cortisone-treated animals had a normal periodicity of GH plasma concentration, but they showed a reduction in values in the range of 50 to 99 ng/ml ($P < 0.01$) and an increase of values in the range of 200 to 499 ng/ml ($P < 0.025$) and above 1000 ng/ml ($P < 0.05$). The area under the GH concentration curve of the cortisone-treated rats was significantly greater than that of the controls, 100.9 ± 18.7 (mean ± SE) units vs 55.3 ± 7.4 ($P < 0.025$). Thus, increased growth hormone secretion during the light phase persisted in spite of failure of catch-up growth acceleration. The findings indicate that the mechanism involved in GH release is linked to the catch-up growth control.
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Failure of catch-up growth acceleration has been observed following a short period of cortisone injections in rats (1). Immunoassayable growth hormone (GH) concentration in plasma obtained from gentled decapitated rats tends to be elevated long into the recovery period after cortisone injections (2). Metabolic clearance rate of GH is persistently lower in cortisone-treated rats during recovery than in controls but this can be attributable to reduced soft tissue mass and a consequent reduction in number of GH receptors (3). The present studies were initiated to confirm that the increased plasma GH levels during recovery are due to increased secretion and to determine the pattern of secretion of GH during the recovery period.

Materials and Methods. Male rats of the Long–Evans strain were obtained at 35 days of age from Simonsen Laboratories, Inc. (Gilroy, Calif.), and were housed one to a cage in an environment of fresh filtered air, 22.2 to 25.6°C, and light/dark periods of 14/10 hr. The diet was Purina Lab Chow and tap water *ad lib.* Cages were stainless steel, the hanging type, 7 × 7 × 10 in in size. The animals were handled by the same two attendants throughout the experiments. Routine handling consisted of once or twice weekly body weight and tail length measurements (4). At 40 days of age the animals were distributed according to body weight into control and experimental groups each having approximately the same mean and variance of body weight. Experimental rats received cortisone acetate injected sc in a dose of 5 mg/rat/day for 4 days beginning at 40 days of age. Control rats were given injections of an equivalent volume of saline, 0.2 ml. The last day of injection was designated as recovery Day 0. On recovery Days 11 to 13 a catheter was implanted into the superior vena cava (5) of the recovering experimental and corresponding control rats. After surgery and before sampling the rats were habituated 2 hr on 2 different days in insulated chambers (Small Universal Cubical BRS/LVE, Tech Serv. Inc., Beltsville, Md.) provided with fresh air flow and routine light/dark cycle. Only one rat within its storage cage with food and water was housed in a chamber. From recovery Days 17 through 27 sampling was carried out in seven cortisone-treated and seven control rats. All rats were placed into the environmental chambers and their

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sampling catheters were attached 11 hr prior to sampling. They remained in the chambers until sampling was completed. Sampling was at 15-min intervals from 06:00 to 18:00, all during the lights-on period.

Plasma GH concentration was determined in duplicate by radioimmunoassay (6). The initial assay was carried out with a reference range of 10 to 250 ng/ml. Samples with values above or below that range were assayed at plasma concentrations corresponding to 40 to 1000 ng/ml or 1.25 to 31.25 ng/ml in order to determine peak height and trough level, respectively. Area under the curve of plasma GH concentration plotted against time was calculated by the trapezoid rule using a program which eliminated intervals following missing values. The incidence of missing values did not differ significantly between cortisone-treated and control rats. Area is expressed as the mean of arbitrary units per sampling interval. The period of GH surges was determined by averaging for each rat the time between every first value above 50 ng/ml after a previous value below 50 ng/ml and the succeeding such values in the record. Differences between means were tested for significance by one-tailed t test.

Results. *Body weight and tail length growth.* Cortisone injections caused prompt decrease in growth rate of body weight and slower decline in tail length growth. Following the last injection a normal growth rate of body weight and tail length ensued. Body weight growth was slowed transiently following surgical implantation of the catheter. There was no catch-up growth acceleration during the portion of the recovery period spanned by the present observations (Fig. 1).

Plasma GH concentration. Cortisone-treated and control rats had periodic surges of plasma GH concentration which usually extended above 200 ng/ml. In the intervals GH concentration dropped to less than 1.0

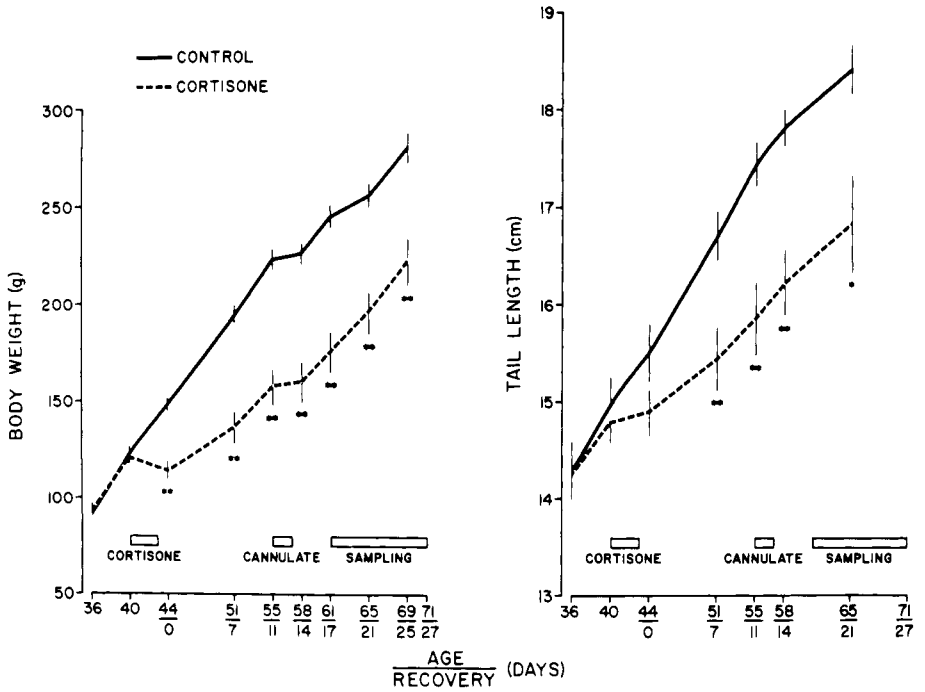

FIG. 1. Body weight and tail length growth curves of the controls and cortisone-treated rats. All data points except the last tail length values are means of seven rats. The last tail length values are means of six rats in each group. Vertical bars represent SE. Asterisks indicate points with significant differences between means of the controls and cortisone-treated rats ($*P < 0.001$, $**P < 0.005$).

TABLE I. RANGES OF GH CONCENTRATION (ng/ml)

	N	0–49	50–99	100–199	200–499	500–999	>1000
Control	7						
Mean		36.4	5.3	3.3	2.7	1.0	0
SE		1.8	0.7	0.6	0.5	0.2	0
Cortisone	7						
Mean		35.3	2.9	3.1	5.3	1.6	0.9
SE		1.2	0.4	0.6	0.9	0.5	0.5
P		NS	<0.01	NS	<0.025	NS	<0.05

ng/ml in both cortisone-treated and control rats. The pattern of surges appeared no different between cortisone-treated and control rats (Fig. 2). The mean periods of the growth hormone surges were 3.0 ± 0.06 hr for cortisone-treated rats and 3.1 ± 0.14 hr for controls (mean ± SE), an insignificant difference.

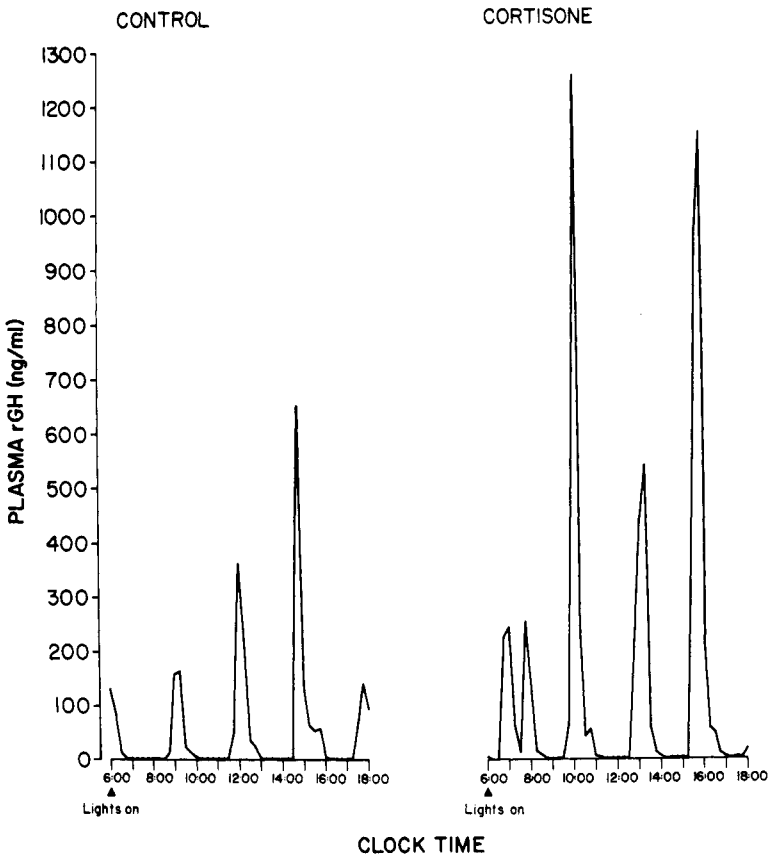

FIG. 2. Plasma GH concentration determined at 15-min intervals over a 12-hr period in a control rat and a cortisone-treated rat. The area under the curve of GH concentration vs time in units/15 min (see text) is 52 in the control rat and 133 in the cortisone-treated rat. The figure illustrates the normal pulsatile pattern of plasma GH concentration in the cortisone-treated rat.

The average area per 15-min interval under the GH curve was 100.9 ± 18.7 (mean ± SE) units in cortisone-treated rats vs 55.3 ± 7.4 in controls ($P < 0.025$).

Cortisone-treated rats had no change in the number of values of GH concentration in the range of 0 to 49 ng/ml. In the range of 59 to 99 ng/ml the cortisone-treated rats had a reduced number of values ($P < 0.01$), however, they had an increased number in the range of 200 to 499 ng/ml ($P < 0.025$) and above 1000 ng/ml ($P < 0.05$) (Table 1).

Discussion. The absence of catch-up growth observed in the cortisone-treated rats in the present experiment is typical of this experimental model (1). The finding of increased GH secretion during the recovery period corroborates our previous finding of elevated plasma GH concentration in trunk blood of similarly treated rats (2). The results show in addition, that the increased secretion occurs within a pulsatile pattern characterized by normal periodicity and by surges with greater than normal peak values separated by troughs having values < 1.0 ng/ml. The findings support our earlier conclusion that changes in metabolic clearance rate alone could not account for the higher plasma GH concentration found in recovering cortisone-treated rats (3).

In recovering fasted rats undergoing brisk catch-up growth we have also found increased GH secretion occurring within a normal pulsatile pattern (7). That study included 24-hr sampling periods which provided data showing that the increased GH secretion occurred within only the lights-on period which corresponds to the inactive phase in the rat (8). It is of interest that the increased GH pulsatile secretion observed in the recovering cortisone-treated rat also occurs within the normal pulsatile secretory rhythm. Since blood samples were not obtained during the dark (active) phase in the present experiments, the diurnal patterns of GH secretion of the fasted and cortisone-treated rats cannot be compared. The occurrence of increased GH secretion in both the fasted and cortisone-treated models supports the possibility that the GH secretory mechanism is linked to the catch-up growth control. The absence of catch-up growth acceleration in the face of increased GH secretion in the cortisone-treated rat is consistent with the hypothesis that the failure of catch-up growth in the recovering cortisone-treated rat is due to a failure of response of target tissues to growth factors (9, 10).

Although catch-up growth is a commonly observed phenomenon, the mechanism is as yet unknown. An attractive hypothesis proposes a central control for catch-up growth which involves at least three components: a sensor for existing body size, a stimulator for increased growth rate, a reference (set-point) for normal body size for ages (11–13). That the increased GH secretion is constrained to the normal pulsatile rhythm and that it is entrained to the environmental lights-on phase, at least in the fasted rat, suggests that the catch-up growth control is located in the central nervous system. The present results are consistent with the concept that the GH-releasing mechanism is linked to the putative catch-up growth control through the components which sense the discrepancy between actual body size and normal body size for age.

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