Positive Rate-Sensitive Corticosteroid Feedback Mechanism of ACTH Secretion in Cushing's Disease

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Research Article

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Positive Rate-Sensitive Corticosteroid Feedback Mechanism of ACTH Secretion in Cushing's Disease

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A B S T R A C T   To define the nature of the disturbance of the corticosteroid feedback mechanism in Cushing's disease, the dynamic aspects of the ACTH response to corticosteroid administration have been studied in patients with Cushing's disease after total adrenalectomy (C.d. post adx.). The results were compared with those obtained in patients with Addison's disease (control group). Different experimental designs for administration of cortisol were chosen to provide extreme variations in the input signal. The response of the system was evaluated by measuring plasma ACTH concentrations (radioimmunoassay) at short time intervals.

Infusion of cortisol at constant rate (50 mg/h for 2 h) resulted in a transient, paradoxical rise in ACTH levels with a maximum at 15 min. ($315\pm65\%$, mean$\pm$SEM). In contrast, in the control group there was an immediate and rapid decrease in ACTH levels with a significant inhibition after 15 min ($80\pm6\%$, mean$\pm$SEM). Infusion of 50 mg cortisol for 5 and 15 min, respectively, produced an increase in ACTH levels, which was confined to the time when cortisol levels were rising (maximum: $137\pm30\%$ and $139\pm10\%$ at 5 and 15 min, respectively, mean$\pm$SEM). This increase corresponded in time to the first decrease in ACTH levels in the Addisonian patients. With bolus injections of 25 mg cortisol, ACTH levels remained unchanged during the first 15 min. The time-course in the patients with C.d. post adx. was essentially the same as in the Addisonian patients.

From these results it is concluded that in the patients with C.d. post adx. the rapid, rate-sensitive feedback mechanism was converted into a positive one, whereas the delayed, dose-sensitive mechanism was completely undisturbed. The capacity of dexamethasone to activate rate-sensitive feedback elements was markedly diminished. Accordingly, there were only minor positive feedback effects upon ACTH secretion in the patients with C.d. post adx.

INTRODUCTION

The existence of a dual corticosteroid feedback mechanism of stress-induced ACTH secretion in the rat is well established (1–7). A recent study by Kaneko and Hiroshige (8) has amply confirmed the finding of Dallman and Yates (1) that there are two different types of negative feedback inhibition of stress-induced activation of ACTH secretion: (*a*) the fast, rate-sensitive, and (*b*) the delayed, proportional feedback inhibition. In accordance with this concept, our own studies upon dynamic aspects of the suppression of ACTH levels by corticosteroids in patients with nonstressed ACTH hypersecretion secondary the hypoadrenocorticism revealed that two phases of suppression were to be differentiated (9). A first decrease occurred without latency whenever and as long as cortisol levels were rising. There was a linear regression between the logarithm of the rate of rise in cortisol concentrations and the decrease in ACTH levels (differential or rate-sensitive feedback mechanism). Neither cortisol doses nor plasma cortisol concentrations were adequate inputs for this rapid mechanism. In these experiments, the rate-sensitive feedback effects of dexamethasone were less than might have been predicted from its relative anti-inflammatory potency. A second decrease in ACTH levels became manifest $\cong$30 min after starting the corticosteroid administration. In this case there was a linear regression between the degree of inhibition of ACTH levels and the cortisol doses (integral or dose-sensitive feedback mechanism).

On the other hand, we demonstrated that in adrenalectomized patients with Cushing's disease,

TABLE I
TABLE I
Clinical Data of the Patients with C.d. post adx.

Case	Sex	Age	Time since adrenalectomy	Abnormal fossa	Plasma ACTH at 8 a.m.
		yr			pg/ml
1	M	36	4 wk	φ	805
2	F	57	12 wk	φ	905
3	F	22	16 wk	φ	660
4	M	14	2 yr	φ	173
5	F	49	2 yr	φ	728
6	F	33	3 yr	φ	295
7	F	20	4 yr	φ	1,625
8	M	42	7 yr	φ	2,300
9	F	48	15 yr	+	916
10	F	39	18 yr	+	2,541

Clinical data of the patients with C.d. post adx. ACTH values were obtained 24 h after the last dose of replacement therapy. In most cases the mean value of several determinations is given. "Abnormal fossa" indicates that a positive, standard anterior-posterior and lateral roentgenogram of the head had been obtained. None of these patients had ever been treated by pituitary irradiation.

cortisol infusions induced a transient paradoxical rise in ACTH levels, with a maximum at 15 min (10). From all these data we suggest that in Cushing's disease the negative rapid feedback mechanism is converted into a positive one, whereas the delayed feedback mechanism remains intact. To test this hypothesis the dynamic aspects of the ACTH response to corticosteroid administration in patients with Cushing's disease after total adrenalectomy (C.d. post adx.)[1] have been studied in more detail. Different experimental designs for administration of cortisol were chosen to provide extreme variations of the input signal; i.e., the magnitude and temporal pattern of cortisol plasma concentrations. The response of the system was evaluated by measuring plasma ACTH concentrations at short time intervals.

METHODS

10 C.d. post adx. patients participated in this study. The clinical data are given in Table I. 23 patients with primary adrenocortical insufficiency (Addison's disease) served as a control group. All patients received a replacement therapy consisting of 37.5 mg cortisone-acetate (25 mg in the morning and 12.5 mg in the afternoon) and 0.1 mg 9-α-fluorohydrocortisone daily. The last dose of both medications had been administered 24 h before the onset of the examination. The studies were performed in the morning hours, starting between 8 and 9 a.m. Cortisol (100 mg free alcohol in 20 ml 50% ethylalcohol; Hydrocortison zur infusion, Hoechst AG, Frankfurt, West Germany) was infused according to different

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[1] *Abbreviation used in this paper*: C.d. post adx., Cushing's disease after total adrenalectomy.

experimental designs: protocol 1, constant rate infusion of 50 mg cortisol/h for 2 h, with a Braun perfusor; protocol 2, infusion of 50 mg cortisol during 5 min at a constant rate; protocol 3, infusion of 50 mg cortisol during 15 min at a constant rate; protocol 4, bolus injection of 25 mg cortisol. In some cases dexamethasone-21-orthophosphate (Fortecortin-mono-ampullen, Merck AG, Darmstadt, West Germany) was given intravenously. Either 1.25 mg/h was infused at a constant rate for 2 h, or 1.0 mg was given as bolus injection. Dexamethasone doses were chosen with respect to their antiinflammatory potencies; dexamethasone was considered to be 30 times more potent than cortisol (11).

Blood was drawn through an indwelling cannula at 5- or 15-min intervals. Plasma ACTH was estimated by radioimmunoassay after extraction of ACTH from the plasma as previously described (12, 13). Because of the large variation of the starting levels, all values have been calculated as a percentage of the individual mean base-line values. Plasma cortisol measurements were performed by competitive protein binding assay (14).

Statistical analysis. To describe the time-course of plasma ACTH in response to corticosteroid administration, two neighboring points of each curve (usually the 0- and 15-min values) were selected and tested by the Student's *t* test for paired data (15). As only this segment of the curves was important for testing the hypothesis, we did not attempt to describe the whole curves by statistical analysis.

RESULTS

Plasma cortisol concentrations after intravenous administration of cortisol according to the different protocols are depicted in Fig. 1. There were no significant differences between plasma cortisol concentrations in the patients with C.d. post adx. and the patients with Addison's disease at any time of the observation period. Therefore, the mean values in Fig. 1 have been calculated from the individual values of both groups.
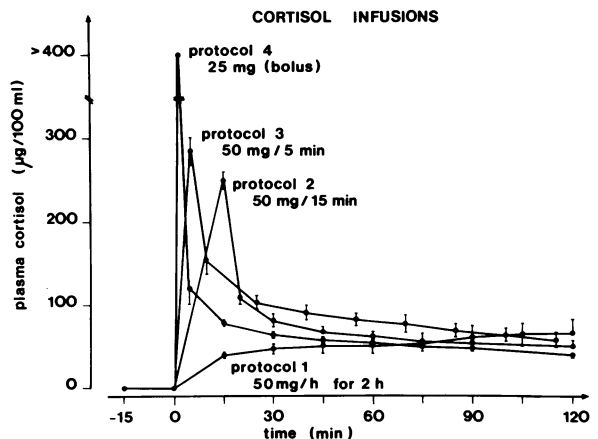

FIGURE 1 Time-course of plasma cortisol concentrations in response to intravenous administration of cortisol according to different protocols. There were no significant differences between plasma cortisol concentrations in the patients with C.d. post adx. and the patients with Addison's disease at any time of the observation period. Therefore the mean values in this figure have been calculated from the individual values of both groups. The vertical bars indicate ±SEM, *n* = 33.

The amounts of ethyl alcohol necessary in these experiments to dissolve cortisol were shown to be without effect on ACTH plasma levels. Starting ACTH levels in all patients 24 h after the last dose of the usual replacement therapy were markedly elevated (C.d. post adx.: 1,095±254 pg/ml; mean±SEM; Addison's disease: 1,830±396 pg/ml; mean±SEM; normal range: 0–150 pg/ml). There were no significant differences in the starting values between both groups ($P > 0.05$). When cortisol was infused at a constant rate for 2 h (protocol 1) to patients with C.d. post adx., there was an immediate, transient rise in ACTH levels, with a maximum at 15 min (315±65%; mean±SEM) (Fig. 2). The difference between this value and the starting value was significant ($P < 0.01$). Later, ACTH levels decreased but did not fall below starting levels until 90 min after starting the cortisol infusion. In contrast, in the control group (patients with Addison's disease) there was an immediate and rapid decrease in ACTH levels, which continued throughout the infusion period. The difference between ACTH values at 15 min (80.2±5.8%; mean±SEM) and the starting values was significant ($P < 0.025$).

The changes in plasma ACTH after bolus injection of 25 mg cortisol to patients with Addison's disease and patients with C.d. post adx. are depicted in Fig. 3. There were no marked differences between both groups at any time of the observation period. In contrast to the striking differences obtained with protocol 1 during the first 15 min, there was no decrease in ACTH levels in the Addisonian patients and no increase in the patients with C.d. post adx. In fact, ACTH levels remained essentially unchanged during the first 15 min.

FIGURE 3 Time-course of plasma ACTH levels in response to bolus injections of 25 mg cortisol in patients with C.d. post adx. and Addison's disease.

Protocol 2 and 3 (infusion of 50 mg cortisol for 5 and 15 min, respectively) produced a sharp increase in cortisol concentrations for a limited time period (5 and 15 min, respectively). These protocols, applied to Addisonian patients, induced a first rapid decrease in ACTH levels, which was confined to the time during which cortisol levels were increasing (Figs. 4 and 5). Immediately after cessation of the cortisol infusion ACTH levels in Addisonian patients rose again, with a maximum 5 min later. Thereafter, a second decrease in ACTH levels was demonstrable. In patients with C.d. post adx. there was an increase in ACTH levels which corresponded exactly to the first decrease in ACTH levels observed in the Addisonian patients and hence to the increase in plasma cortisol con-
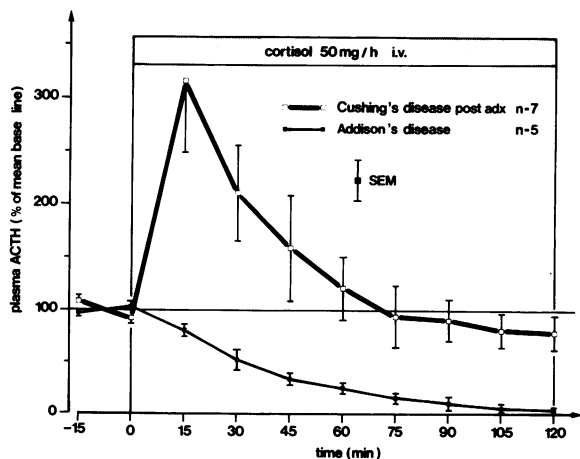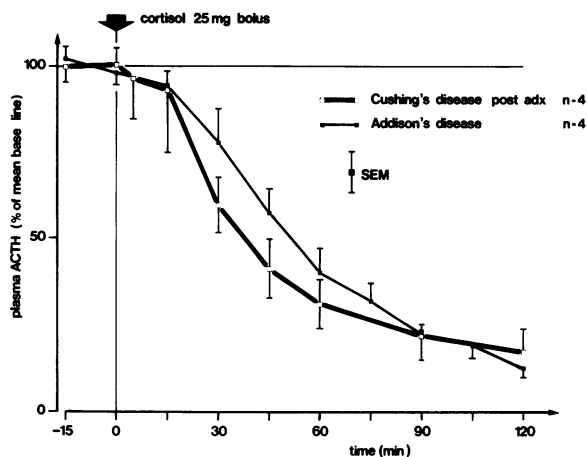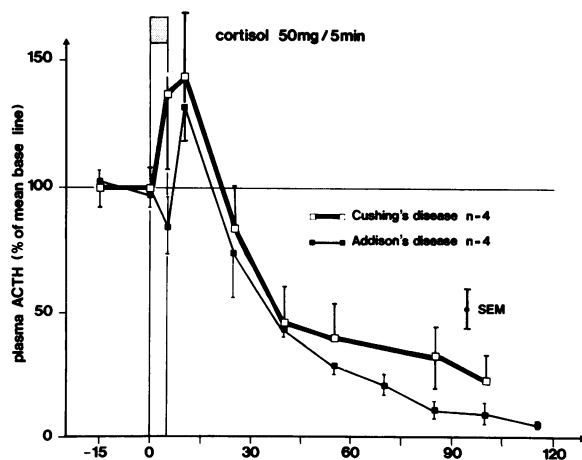

FIGURE 2 Time-course of plasma ACTH levels in response to an infusion of 50 mg cortisol/h at a constant rate for 2 h in patients with C.d. post adx. and Addison's disease. Because of the large variations in starting levels, all ACTH values have been calculated as percentage of the individual mean base-line values.

FIGURE 4 Time-course of plasma ACTH in response to an infusion of 50 mg cortisol during 5 min in patients with C.d. post adx. and Addison's disease.

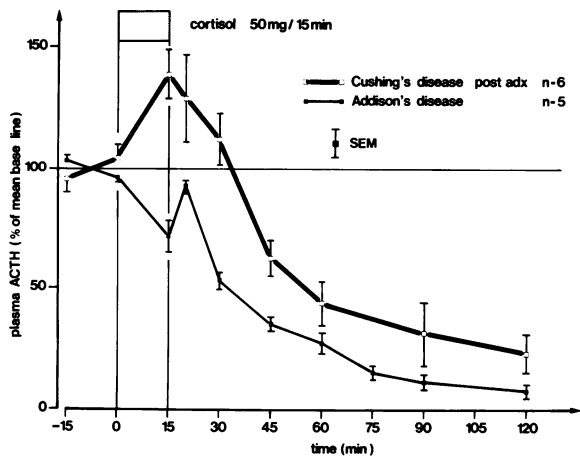*H. L. Fehm, K. H. Voigt, G. Kummer, and E. F. Pfeiffer*

FIGURE 5 Time-course of plasma ACTH levels in response to an infusion of 50 mg cortisol during 15 min in patients with C.d. post adx. and Addison's disease.
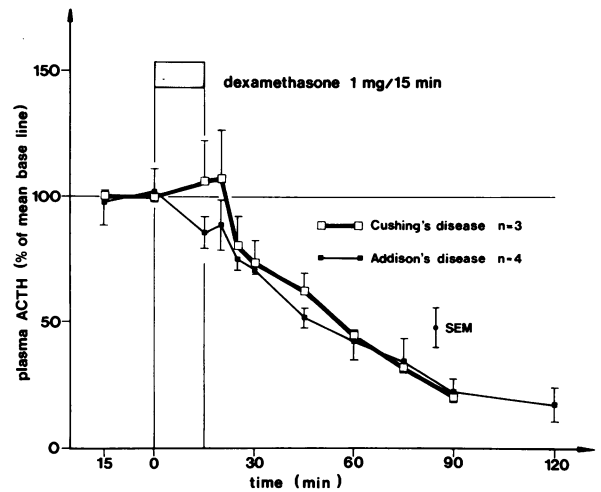

FIGURE 6 Time-course of plasma ACTH levels in response to an infusion of 1 mg dexamethasone during 15 min in patients with C.d. post adx. and Addison's disease.

centration. 5 min after cessation of the cortisol infusion, a decline in ACTH levels occurred which was similar to the time-course of ACTH levels in the Addisonian patients. The increase in ACTH levels achieved with protocol 3 (50 mg cortisol/15 min) in patients with C.d. post adx. was significant (15-min values vs. corresponding starting values, $P < 0.01$) as was the decrease observed in the control group (15-min values vs. corresponding starting values, $P < 0.01$). The paradoxical increase in ACTH levels achieved with 50 mg cortisol during 15 min (139±10%; mean±SEM) was remarkably less than that observed with 50 mg cortisol/h (315±65%; mean±SEM), although in this latter case only 12.5 mg cortisol had been infused during the first 15 min. Protocol 2 (50 mg cortisol/5 min) yielded no significant differences (5-min values vs. corresponding starting values).

1 mg dexamethasone infused during 15 min induced a slight, insignificant decrease in ACTH levels at 15 min in the patients with Addison's disease (Fig. 6). Accordingly, in the patients with C.d. post adx. there was only a slight, insignificant increase. When dexamethasone was infused at a constant rate during 2 h (1.25 mg/h) (Fig. 7), the time-course of ACTH levels in patients with C.d. post adx. was similar to those obtained with 50 mg/h cortisol. However, maximal stimulation at 15 min was less pronounced (228±51% vs. 315±65%; mean±SEM).

DISCUSSION

Cushing's disease is characterized by a transient paradoxical increase in ACTH secretion in response to corticosteroid administration (10). These studies indicate that this paradoxical increase is restricted to the time when plasma cortisol concentrations are rising, corresponding to the period of action of the

rapid, rate-sensitive feedback mechanism, which can be observed in Addisonian patients (9). It can be concluded that in Cushing's disease the normally negative rate-sensitive feedback mechanism is converted into a positive one. With bolus injections of cortisol, the time of increase in plasma cortisol was too short to activate rate-sensitive feedback elements in the Addisonian patients. Similarly, there was no increase in ACTH secretion in patients with C.d. post adx. Thus, this protocol enabled observation of the delayed, dose-sensitive feedback mechanism solely. It appeared that the dose-sensitive corticosteroid feedback mechanism was completely undisturbed in the patients with Cushing's disease. With all other protocols, both feedback elements overlapped temporally, which resulted in different temporal patterns for increase and
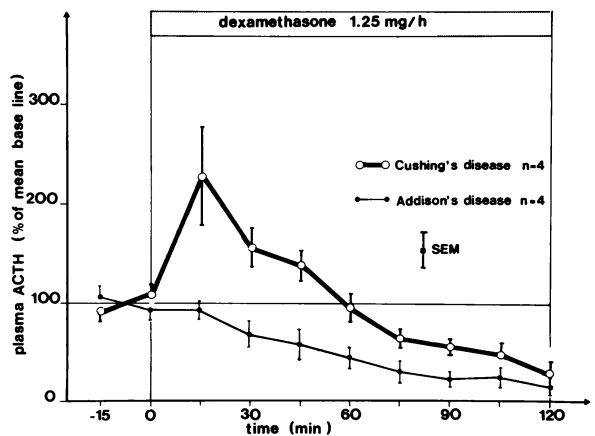

FIGURE 7 Time-course of plasma ACTH levels during infusions of 1.25 mg dexamethasone/h at a constant rate for 2 h on patients with C.d. post adx. and Addison's disease.

decrease of plasma ACTH levels. The optimal conditions for demonstration of the positive rate-sensitive feedback mechanism in Cushing's disease were achieved with protocol 1 (administration of 50 mg cortisol/h) by which means a long lasting increase in cortisol concentrations had been produced.

In the case of dexamethasone, its relative anti-inflammatory potency had to be considered. The capacity of these small doses (1.0 or 1.25 mg) to activate rate-sensitive feedback elements was very weak in the Addisonian patients. Similarly, positive feedback effects upon ACTH secretion in the patients with C.d. post adx. were small or absent. That dexamethasone is ineffective in triggering rapid feedback is consistent with the unpublished observation cited by Yates and Maran (16) and with a previous report by Abe and Critchlow (7).

However, in vitro results reported by Jones and Hillhouse (17) are contradictory. These authors incubated rat hypothalami and found a rapid inhibition of corticotropin-releasing factor release stimulated by acetylcholine, when acetylcholine and dexamethasone were added simultaneously. The basis for the difference in results obtained with these in vivo and in vitro approaches is unknown.

Earlier studies upon suppressibility of ACTH secretion by corticosteroids in Cushing's disease yielded conflicting results (18–20). However, as the dynamic aspects of the feedback mechanism have not been taken into account in these studies, the differences may be attributed to this fact.

Patients with active Cushing's disease are resistant to the suppressive influence of small doses of dexamethasone (2 mg/d), and this forms the basis for the classical dexamethasone suppression test (21). The results of this test suggest that there are differences in dose-sensitive feedback effects between patients with and those without Cushing's disease. Consequently it is surprising that no such differences were observed in our studies. There are several possible explanations for this discrepancy. (a) The doses of cortisol and dexamethasone used in our experiments were so large that the difference in threshold between both groups was not evident. (b) The results of the dexamethasone suppression test in patients with active Cushing's disease may not reflect the activation of dose-sensitive feedback elements but may depend upon the suppression of positive, differential feedback effects of the endogenous cortisol by the integral feedback effects exerted by dexamethasone. (c) Overall, the situation in patients with untreated hypersecretion of endogenous cortisol is so different from those in the patients of our study, which were glucocorticoid deficient, that comparisons should be made cautiously. Further studies are necessary to answer these questions.

There are a number of case reports of a paradoxical rise in urinary steroid excretion during the dexamethasone suppression test in patients with untreated Cushing's disease (22–25). In all our patients, however, suppression of adrenocortical function by 8 or 12 mg dexamethasone had been demonstrated before adrenalectomy. Therefore, it is unlikely that the phenomenon of the positive rate-sensitive feedback mechanism is related to the rare finding of a paradoxical rise in urinary steroid excretion during the dexamethasone suppression test. Furthermore, from our results, dexamethasone would not be expected to produce such effects because of its limited capacity to activate rate-sensitive feedback elements.

These studies offer no information regarding the site of action of rapid feedback and hence the structures responsible for its disturbance in Cushing's disease. Abe and Crichlow (7) demonstrated that rapid feedback persists in rats subjected to surgical isolation of the medial basal hypothalamus. Therefore it was assumed that the site of action is within the medial basal hypothalamus-pituitary unit. These results are consistent with the conclusion of Jones et al. (26) that the primary site of rapid feedback is the hypothalamus. However, we demonstrated (27) both rapid rate-sensitive and delayed dose-sensitive feedback suppression by corticosterone of the ACTH response of isolated pituitary cells to median eminence extracts. Therefore, it remains to be determined whether either both of these feedback effects reflect hypothalamic or pituitary or both sites of action.

Furthermore, extrahypothalamic sites may be involved in the negative feedback regulation of ACTH release. Rotsztejn et al. (28) studied the relationship between ACTH release and corticosterone binding by the receptor sites of the adenohypophysis and dorsal hippocampus in rats. The authors inferred from their findings that specific adenohypophyseal binding sites may be chiefly involved in the tonic regulation of ACTH secretion; equally specific high-affinity hippocampal receptors may play a role in the transient adjustment of pituitary-adrenocortical activity. DeKloet et al. (29) presented evidence for more than one population of corticosteroid-binding sites in brain and anterior pituitary. They suggested that whereas corticosterone binds preferentially in the hippocampus, dexamethasone shows a preference for binding in the pituitary. It is possible that the different effects of these two steroids on rate-sensitive and delayed feedback reflect these different primary sites of action.

Recently, Kaneko and Hiroshige (30) examined the site of action of the fast, rate-sensitive feedback inhibition of ACTH secretion under stress in rats, using the corticotropin-releasing factor activity of the median eminence as an indicator. The results suggested that

this mechanism operates at or above the level of the corticotropin-releasing factor neurons in the hypothalamus. Furthermore, in rats whose brain catecholamines had been depleted by intraventricular injection of 6-hydroxydopamine, the rate-sensitive mechanism was eliminated while the delayed component was left intact. These results imply that the site of action of fast, rate-sensitive feedback inhibition is located in the central nervous system, probably in close association with catecholaminergic neurons.

This would implicate that the site of disturbance of the corticosteroid feedback mechanism in Cushing's disease is at or above the hypothalamus. The evidence put forth by Krieger et al. (31–34) that Cushing's disease is a central nervous system disorder is in favor of such an assumption.

On the other hand, it is established that complete cure of Cushing's disease can be obtained in most patients with selective removal of a microadenoma from the pituitary gland (35, 36). The current experience with this microsurgical procedure would suggest a pituitary origin of Cushing's disease, and that hypothalamic abnormalities of ACTH regulation are a consequence of hypercortisolism rather than a manifestation of a primary central nervous system disorder. At this moment it is impossible to decide this question when all arguments for one or the other hypothesis are taken into account (37).

Finally, we would like to point out that the conversion of a negative feedback mechanism into a positive one is a common feature in certain fields of endocrine physiology and pathophysiology. As early as 1934 a stimulatory effect of gonadal steroids on gonadotrophin secretion has been demonstrated by Hohlweg (38) in immature rats. Later, it has been possible to provoke a premature release of gonadotrophins in the intact cycling rat by injections of estrogen on the day of estrus (39). Similarly, there are several abnormal states which are associated with a paradoxical response of plasma growth hormone to glucose loading (40).

ACKNOWLEDGMENTS

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