Natural History of Pituitary-Adrenal Recovery Following Long-Term Suppression with Corticosteroids

ALAN L. GRABER, ROBERT L. NEY, WENDELL E. NICHOLSON, DONALD P. ISLAND, AND GRANT W. LIDDLE
Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

ABSTRACT. Plasma ACTH and 17-hydroxycorticosteroid concentrations were measured at various intervals in patients recovering from prolonged pituitary suppression. Pituitary-adrenal recovery was found to follow a definite pattern requiring several months for completion. Initially, both ACTH and corticosteroid levels were relatively low, a situation similar to that seen in patients with hypopituitarism. Thereafter, plasma ACTH levels gradually increased until they were supernormal, but there was a lag of several months in the recovery of normal adrenal responsiveness. Despite the fact that the pituitary gland could secrete large quantities of ACTH and despite the fact that corticosteroid levels were subnormal, a diurnal rhythm was observed in ACTH levels with a decrease to low values during the latter portion of each day. After several months, corticosteroid levels rose to normal, and soon thereafter plasma ACTH concentrations fell again to normal. (J Clin Endocrinol Metab 25: 11, 1965).

FOR MANY years it has been known that, in a patient with Cushing’s syndrome due to an autonomously functioning adrenocortical tumor, the cortisol produced by the tumor suppresses the secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland and thereby induces atrophy and unresponsiveness of the patient’s nontumorous adrenal tissue (1). Prior to the availability of synthetic cortisol, it was almost impossible to effect a cure of Cushing’s syndrome due to adrenal tumor because of the likelihood that the patient would die of adrenal insufficiency if the tumor were completely excised (2, 3). Similar suppression of pituitary-adrenal function occurs during prolonged administration of supraphysiologic doses of cortisol-like steroids and constitutes one of the serious unsolved problems associated with the pharmacologic use of corticosteroids (4, 5).

Previous knowledge relating to pituitary-adrenal suppression following prolonged corticosteroid administration has been well summarized by Paris (6). Attempts to understand the nature of the pituitary-adrenal failure after prolonged suppression have been interpreted in various ways. Some investigators have suggested that endogenous ACTH production is severely limited for prolonged periods (7), and reduction in pituitary ACTH content has been noted after prolonged corticosteroid treatment (8). Others have emphasized the importance of adrenal atrophy and unresponsiveness to ACTH (9–11). Histopathologic changes in both the pituitary and adrenal glands have been described (12).

The present study was designed to clarify the natural history of the recovery of pituitary-adrenal function following...
long-term suppression with corticosteroids. Selected for study were patients who had received or secreted supra-physiologic quantities of corticosteroids continuously for at least one year and who had developed clinical features of Cushing’s syndrome. “Recovery” was considered to have begun when the Cushing’s syndrome was cured, either by total removal of the adrenal tumor or by discontinuation of treatment with exogenous steroids. The “natural history” of recovery of pituitary-adrenal function was studied simply by obtaining serial measurements of plasma 17-hydroxycorticosteroids and plasma ACTH. This elementary approach has not been employed in previous studies.

Materials and Methods
Clinical. Fourteen patients were studied. Eight had Cushing’s syndrome due to adrenocortical tumors, which were totally excised. The other 6 patients had been treated with supraphysiologic doses of exogenous corticosteroids for periods of 1–10 years for conditions such as ulcerative colitis, rheumatoid arthritis and hypoglycemia. In correcting the hypercorticism of the patients in this study, it was necessary to reduce steroids gradually (over periods of 1–4 weeks) in order to avoid severe manifestations of steroid withdrawal (13).

After steroids had been completely discontinued, the recovery of pituitary-adrenal function was assessed by measurements of plasma 17-hydroxycorticosteroids and plasma ACTH. In 6 of the patients, repeated measurements were performed over periods of several months; in the others, single observations were made. Adrenocortical responsiveness was tested by administering ACTH, 50 U iv over an 8-hr period, and measuring the resulting increases in plasma and urinary 17-hydroxycorticosteroids.

Laboratory Methods. Plasma ACTH was extracted and assayed by methods previously described (14, 15). Plasma (16) and urinary (17) 17-hydroxycorticosteroids were measured by modifications of the method of Silber and Porter.

Results and Comments
The normal relationship between plasma 17-hydroxycorticosteroid concentrations and plasma ACTH concentrations has been studied previously (14) and is represented graphically in Fig. 1. At 6:00 AM plasma ACTH values are normally found in the neighborhood of 0.1 to 0.4 mU/100 ml and plasma 17-hydroxycorticosteroids in the range of 12 to 25 μg/100 ml. There is a diurnal rhythm in pituitary-adrenal function, and both ACTH and steroid levels fall as the day advances. In making comparisons between groups of patients, therefore, it is necessary to take into account the hour at which specimens are obtained. In this study, unless otherwise indicated, all specimens were obtained at 6:00 AM.

Patients with Cushing’s syndrome due to exogenous cortisol or to the autonomous production of cortisol by an adrenal tumor were found, prior to correction of their Cushing’s syndrome, to have elevated plasma 17-hydroxycorticosteroid levels and subnormal plasma ACTH. Following the correction of the cortisol excess, a definite pattern of pituitary-adrenal recovery was observed (Fig. 1).

Phase I. During the first month after the correction of pituitary-adrenal suppression, the patients exhibited various clinical manifestations of mild adrenal insufficiency, including weakness, malaise, anorexia, nausea, aching in joints and muscles, and despondency. Plasma and urinary 17-hydroxycorticosteroid levels were subnormal, and adrenal responses to standard test doses of ACTH were distinctly subnormal. Despite the obvious steroid deficiency, plasma ACTH concentrations remained relatively low. Thus, unlike addisonian patients, who develop high plasma levels of ACTH when cortisol levels are low (18),
these patients failed to respond to steroid deficiency with increased ACTH secretion. They behaved, instead, like patients with hypopituitarism. In this phase of their convalescence, therefore, our patients had adrenal glands that were relatively unresponsive to ACTH and pituitary glands that were relatively unresponsive to steroid deficiency.

**Phase II.** During the second, third, fourth and fifth months of our patients’

---

**Fig. 1.** Correlation of simultaneous measurements of 6:00 AM plasma 17-hydroxycorticosteroids and plasma ACTH in normal subjects and in patients studied during various stages in their recovery from prolonged pituitary-adrenal suppression. X = normal subjects; • = chronically suppressed patients.
convalescence, plasma ACTH concentrations rose to normal and in most cases to supernormal values; but their plasma 17-hydroxycorticosteroids and adrenal responses to standard test doses of ACTH remained subnormal. In other words, recovery of adrenocortical function lagged behind the recovery of pituitary function.

It was of interest that in this phase of convalescence the patients exhibited a diurnal rhythm in plasma ACTH concentration, which was qualitatively similar to that observed in normal subjects (14). In other words, these patients were capable of developing high levels of ACTH in the morning; yet, in spite of subnormal corticosteroid levels, plasma ACTH concentrations spontaneously fell to low values later in the day.

If the high 6:00 AM ACTH levels had been maintained throughout the 24-hour day, the corticosteroid deficiency would have been corrected quickly. This was accomplished experimentally for one patient during his fifth month of convalescence (Fig. 2). The patient received a constant intravenous infusion of ACTH at the rate of 0.1 U/hr, which maintained his plasma ACTH concentration at the 6:00 AM level of 0.7 mU/100 ml throughout the 24-hour period. By the end of the day plasma and urinary 17-hydroxycorticosteroids had risen to high-normal values.

A similar diurnal rhythm in plasma ACTH concentration was observed in all four patients in whom appropriate studies were performed. Despite the fact that these patients were capable of secreting large quantities of ACTH, and despite their apparent “need” for ACTH (corticosteroid levels were subnormal), ACTH secretion diminished considerably during the latter portion of each day. If it had not been for the diurnal fall in ACTH secretion, it seems probable that recovery of adrenal function would have occurred much more rapidly than it actually did.

The persistent diurnal rhythm in ACTH secretion is not unique to patients recovering from pituitary-adrenal suppression. It plays a prominent role in normal pituitary physiology (14) and has also been found to be characteristic of addisonian patients with subnormal corticosteroid levels (19).

**Phase III.** During the sixth to ninth months of convalescence, the plasma and urinary 17-hydroxycorticosteroids of our patients finally returned to normal. Adrenal responsiveness could not be considered normal, however, since in some patients normal levels of 17-hydroxycorticosteroids occurred only in association with supernormal levels of ACTH.

**Phase IV.** Patients studied nine months or more after the correction of pituitary-adrenal suppression were found to have normal levels of plasma ACTH, normal
plasma and urinary 17-hydroxycorticosteroids, normal adrenal responses to test doses of ACTH, and normal pituitary-adrenal responses to methypyracol (20).

The uniformity of the pattern of pituitary-adrenal recovery is illustrated in Fig. 3, depicting serial assay data on the four most intensively studied patients. After correction of the hypercorticism, each patient passed successively through the previously described phases toward normal. Although considerable variation in the speed of events was encountered, the same pattern of recovery was observed in all.

Discussion

This study indicates that, following profound and prolonged suppression of ACTH, there is a considerable period during which the pituitary gland secretes relatively little ACTH even though corticosteroid levels are deficient. Even after the pituitary gland has resumed the secretion of comparatively large quantities of ACTH, the adrenal glands usually lag for several months in recovering a normal degree of responsiveness. Apparently one factor that tends to delay complete adrenocortical recovery is the decrease in ACTH secretion that occurs during the latter part of the day even though corticosteroid levels are subnormal.

The subject of pituitary-adrenal suppression and recovery has many aspects, and it should be emphasized that the patients selected for this particular study had undergone complete and continuous pituitary-adrenal suppression for at least one year prior to correction of their hypercorticism. It is possible that other results might have been obtained if the period of suppression had been brief rather than prolonged, if pituitary-adrenal suppression had been incomplete rather than profound, if suppression had been intermittent rather than continuous, or if ACTH had been administered frequently during the period of suppression or during the period of convalescence. All these variables merit further consideration, and, until they are investigated, to extrapolate the conclusions derived from this group of patients beyond the conditions of the present study would not be warranted.

References


---

**Notice**

**Purified Radioactive Steroids Available**

The Endocrinology Study Section, Division of Research Grants, National Institutes of Health, has purified radioactive steroids available for distribution to qualified investigators, free of charge except for $5.00 per ampule to cover handling and shipping. Please refer to the complete list of materials available on the cover following the last page in the current issue of *Endocrinology*.

**Purified Pituitary Hormones Available**

The Endocrinology Study Section, Division of Research Grants, National Institutes of Health, has highly purified pituitary hormones for distribution free to qualified investigators. Please refer to the complete list of materials available on the cover following the last page in the current issue of *Endocrinology*. 