The safe and effective recent advances in the neurosurgical management of pituitary diseases have undoubtedly increased the exposure of the neurosurgeon to endocrine disorders. The rapid progress being made in the field of neuroendocrinology will, in all probability, increase the overlap between endocrinological and neurosurgical patient care.

The objective of this article is to present to the neurosurgeon an update on the endocrine approach to hypothalamic-pituitary diseases. To fulfill this objective, we intend to present briefly a review of the present knowledge of the hypothalamic-pituitary endocrine axis, its physiology and pathophysiology, and to discuss in some detail the standard approaches to the diagnosis of its disorders.

FUNCTIONS OF THE HYPOTHALAMIC-PITUITARY ENDOCRINE UNIT

Endocrine Functions of the Hypothalamus

The endocrine functions of the hypothalamus are subserved by two systems of neuroendocrine cells: the neurohypophyseal system, consisting of the supraoptic and paraventricular nuclei, and the tuberohypophyseal system, comprised of certain nuclei, mainly in the medial basal hypothalamus, the hypophysiotropic area.

The Neurohypophyseal System

The neurohypophyseal system is described elsewhere. The cell bodies of the supraoptic and paraventricular nuclei synthesize the octapeptides, antidiuretic hormone (ADH), and oxytocin, in association with specific carrier proteins, the neurophysins. The secretory granules migrate along the axons, through the median eminence, pituitary stalk, and into the posterior lobe of the pituitary gland, where they are stored in perivascular nerve endings. There they remain in storage until they are released by an action potential arising in the cell bodies. The hormones are freed from their carrier proteins at the time of secretion.

Antidiuretic Hormone Vasopressin. The normal physiological functions of ADH are confined to the kidney, the site of action being the distal and the collecting tubules of the nephron. It increases the permeability of this segment of the nephron to water, and water reabsorption can then occur under the osmotic influence of the hypertonic renal medulla. Antidiuretic hormone is an integral part of the homeostatic mechanism that controls water balance.
and effective blood volume (Figs. 1 and 2). The neurohypophyseal nuclei receive input from osmoreceptors which are believed to lie in or around the supraoptic nuclei, from volume receptors located in the left atrium and pulmonary veins, and from the renin-angiotensin system through the circulating levels of angiotensin II. The secretion of ADH is related to other mechanisms that are important for the maintenance of the constancy of the internal milieu, notably the thirst mechanism. An increase in plasma osmolality, through osmoreceptor stimulation, or a decrease in effective blood volume through volume receptor stimulation and through increase in circulating angiotensin II levels, lead to a homeostatic increase in ADH secretion, and thus to renal water conservation. These stimuli also activate thirst, and thus cause increased water intake. These adjustments tend to restore plasma osmolality to normal, and, in conjunction with other homeostatic mechanisms, help to restore effective blood volume. The converse occurs in response to a decrease in plasma osmolality or an increase in blood volume. It is important to remember that “effective blood volume” needs to supersede those of osmotic regulation. Thus, hemorrhage will trigger ADH release even in the presence of plasma hypo-osmolality.
In addition, ADH secretion is also influenced by emotional factors and physical stress. These influences probably operate via neural connections of the neurohypophyseal system with the limbic system, midbrain, and cerebral cortex.

*Oxytocin.* Oxytocin is synthesized predominantly by the paraventricular nuclei, in association with a specific neurophysin. Its known physiological functions relate to reproduction. It has a selective and potent effect on the smooth muscles of the uterus and the mammary glands. Although oxytocin does not seem to be crucial to the initiation and the maintenance of labor, yet it plays a role in the expulsion of the fetus and placenta, since in its absence labor is prolonged. It also causes the contraction of the myoepithelial cells of the breasts and thus helps in the ejection of milk. In these reproductive functions, the synthesis and release of oxytocin are dependent on appropriate sensory stimuli arising from the genital tract and the nipples.

Recent investigations have raised the possibility that ADH and oxytocin may have other endocrine and behavioral functions. They may play a role in the hypothalamic control of anterior pituitary function, and through effects on cerebral registration, consolidation, and retrieval of information, they may influence behavioral responses to environmental change.

**The Tuberohypophyseal System**

The tuberohypophyseal system consists of nuclear groupings in the medial basal hypothalamus extending anteriorly into the septal and preoptic area, the hypophysiotropic area. Its neuroendocrine cells synthesize and release the hypothalamic regulatory hormones (Table 1) which play a dominant role in the control of anterior pituitary functions. From the median eminence, these regulatory hormones are transported via the portal hypothalamic-pituitary venous system to the anterior pituitary gland, where they regulate the synthesis and secretion of the various anterior pituitary hormones.

The tuberohypophyseal system is controlled by neural and humoral influences. The neural impulses originate, directly or indirectly, from the limbic system, other areas of the cerebral cortex, and from the brain stem. Such neural input is mediated via the release of neurotransmitters at the terminal endings around the hypothalamic nuclei. The humoral influences include, among others, the anterior pituitary hormones, hormones of the target glands, and metabolic fuels such as glucose, amino acids, and fatty acids.

The specific hypothalamic regulatory hormones will be discussed with the corresponding anterior pituitary hormones.

**Endocrine Functions of the Anterior Pituitary Gland**

The anterior pituitary gland secretes at least seven well identified hormones (Table 1). Its cellular specialization allows for independent modulation of hormone secretion. The functions and the control of secretion of each of these hormones will be reviewed briefly.

**Thyrotropin**

Thyrotropin (TSH) is a glycoprotein consisting of two subunits designated alpha and beta subunits. The alpha subunit is common to all the pituitary glycoprotein hormones: TSH, follicle-stimulating hormone (FSH), and luteinizing hormone (LH); it is the beta subunit that confers biological specificity. Under the influence of TSH, the thyroid gland forms two hormones: tetraiodothyronine (T4), and triiodothyronine (T3). These two hormones circulate in two forms, a form bound to certain plasma-binding proteins, and a free form. It is the free hormone that is believed to be biologically active, and it represents 0.05% of circulating T4, and 0.5% of T3. Circulating T4 is derived exclusively from thyroid secretion. Two-thirds of circulating T3 is derived from deiodination of T4 by the peripheral tissues.

Thyrotropin-releasing hormone (TRH) is the known hypothalamus-regulating hormone. It is a tripeptide that is secreted by a wide area of the medial
CNS

HYPOTHALAMUS

SOMATOSTATIN

TRH

ANTERIOR
PITUITARY

T.S.H.

THYROID
GLAND

T4

T3

Fig. 3. Diagram showing the hypothalamic-pituitary-thyroid axis.

basal hypothalamus. It stimulates the release and the synthesis of TSH by the thyrotroph. Its pituitary actions do not appear to be selective, since it also stimulates the release of prolactin.

The secretion of TSH is regulated by a dual mechanism: a negative feedback influence by the thyroid hormones, and a stimulatory influence by TRH (Fig. 3). These two influences interact at the level of the thyrotroph such that a decrease in T4 and T3 increases TSH secretion, while an increase has the opposite effect. The neural control of TRH is not fully understood at this time. Somatostatin inhibits the stimulatory actions of TRH on TSH secretion.

Corticotropin

Adrenocorticotropic hormone (ACTH) is a polypeptide that stimulates the biosynthesis of certain steroids by the adrenal cortex. The adrenal cortex secretes mineralocorticoids principally aldosterone, the glucocorticoid cortisol, and sex steroids, mostly androgens. The secretion of aldosterone is primarily under the control of the renin-angiotensin system and serum potassium levels, with ACTH playing a minor regulatory role. It is the secretion of cortisol that is predominantly under the control of ACTH. In addition, ACTH has some melanocyte-stimulating properties. The hypothalamus exerts its stimulatory influence on ACTH secretion via corticotropin-releasing factors (CRF's) that have not, as yet, been characterized. The secretion of ACTH is controlled by a circadian rhythm and stress mechanisms inherent in the central nervous system (CNS), and by negative feedback from the circulating cortisol (Fig. 4). The circadian rhythm results in highest levels of ACTH in the early morning, and lowest levels in the late evening. The negative feedback is believed to be exerted at the hypothalamic and corticotroph levels. Substantial increases in ACTH secretion occur during stress, irrespective of plasma cortisol level. The neurohumoral control of production of CRF's is not fully understood at this time.

Beta-Lipotropin

Beta-lipotropin hormone (B-LPH) is a polypeptide of which the physiological functions are largely unknown. It does have, among other properties, lipolytic and melanocyte-stimulating actions. It is the parent molecule that contains the structure of beta-melanocyte-stimulating hormone (B-MSH) and the various opioid peptides, the endorphins. It is secreted with ACTH by the corticotroph, and its known regulatory influences in the normal individual are identical with those of ACTH.

Gonadotropins

The glycoprotein hormones LH and FSH control the gametogenic and sex-steroid production functions by the gonads in both sexes. In the adult female, in the follicular phase of the menstrual cycle, FSH controls the development and the maturation of the ovarian follicle, and its secretion of estrogen. A sudden midcycle rise of LH is responsible for ovulation; the maintenance of the corpus luteum and its secretion of estrogen and progesterone are controlled primarily by LH. In the adult male, LH controls testosterone production by the Leydig's cells, and FSH is responsible for growth and development of the seminiferous tubules. Together with testosterone, FSH controls optimal spermatogenic function.

So far only one hypothalamic regulatory hormone for the gonadotropins, gonadotropin-releasing hormone (GnRH), has been isolated, characterized, and synthesized. It is a decapeptide formed in a wide area of the medial basal hypothalamus and the preoptic area. Gonadotropin secretion is under the control of complex mechanisms which include neural and

Fig. 4. Diagram showing the hypothalamic-pituitary-adrenal axis.
Endocrinology in hypothalamic-pituitary disease

humoral feedback systems. The final common pathway of such control appears to be GnRH. In the male (Fig. 5), secretion of gonadotropin is regulated by testicular function through a negative feedback system. Testosterone is the regulator of LH secretion, and inhibin, a polypeptide produced by the Sertoli cell, is the regulator of FSH secretion. The testicular hormones probably act at both the hypothalamic and pituitary levels. In the female (Fig. 6), gonadotropin control includes a negative feedback element by the ovarian steroids. However, there is also an element of positive feedback control as well, since under certain conditions estrogen and progesterone can trigger the release of LH and FSH. The necessary phases of gonadotropin secretion that control the normal menstrual cyclic function and ovulation are brought about by complex integrated CNS-hypothalamic-pituitary steroid mechanisms.

**Growth Hormone**

Growth hormone (GH) is a polypeptide that has no specific target tissue, but acts on virtually all cells of the body. It affects intermediary metabolism, and along with the thyroid hormones, insulin, sex steroids, and cortisol, is necessary for hormonal control of linear growth. The effects of GH on linear growth are believed to be mediated by a group of polypeptides, the somatomedins, generated primarily in the liver under the influence of GH.

The hypothalamus exerts a dual control on GH secretion: the structure of growth-hormone releasing factor (GHRF) is yet to be identified. Somatostatin, the growth-hormone release inhibitory hormone, is a tetradecapeptide. The dominant hypothalamic control is stimulatory (Fig. 7).

The secretion of GH is episodic and labile. Neurogenic mechanisms control a sleep-wake cycle which results in increased bursts of secretion shortly after sleep. Exercise, stress, and levels of metabolic fuels also affect GH secretion. How these various stimuli are integrated is not fully known, but they appear to be mediated by neurotransmitters at the hypothalamic level. It is believed that norepinephrine, dopamine, and serotonin all stimulate GH secretion. Catecholaminergic influences are brought about by both alpha and beta receptor stimulation, with alpha effect stimulating, and beta effect inhibiting, GH release.

**Prolactin**

Prolactin (PRL) is a polypeptide that plays an important role in mammary growth and development of lactation, although other hormones are also necessary for initiation and maintenance of these processes (GH, cortisol, sex steroids, and insulin). In animals, prolactin plays a role in the maintenance of corpus luteum and regulation of sodium and water balance, and has a wide range of metabolic effects. It...
remains to be established whether such actions can be demonstrated in man and whether they will be physiologically important or not.

The hypothalamus exerts a dominantly inhibitory influence on PRL secretion via a PRL-inhibitory factor (PIF), which has an unknown chemical structure. The hypothalamus is also believed to form a PRL-stimulating factor, distinct from TRH (Fig. 8). Like GH, the secretion of PRL is episodic and labile, and is regulated by a sleep-wake cycle leading to increased secretion after sleep. Secretion of PRL is also responsive to many physiological and stressful events. How these events are integrated at the hypothalamic level is not known. Catecholamines, particularly dopamine, inhibit PRL secretion, while serotonin increases it.

**HYPOFUNCTION OF THE HYPOTHALAMIC-PITUITARY ENDOCRINE UNIT**

**Neurohypophyseal Hypofunction**

**Diabetes Insipidus**

Although disturbances in oxytocin secretion probably occur, there is no important clinically identifiable correlate of such a disturbance. Hypofunction of the neurohypophysis involves principally ADH deficiency, and manifests itself as the diabetes insipidus (DI) syndrome.

To be able to conserve water in the face of a threat of negative water balance, as in water deprivation, an individual needs a normal hypothalamus which responds to the hyperosmolar threat by the secretion of ADH, an intact distal nephron that responds to ADH, and a normal hyperosmolar renal medulla that creates a gradient for renal water reabsorption across the distal nephron. A normal thirst center and an intact CNS, capable of sensing thirst and responding to it by voluntary efforts to acquire water, can restore water balance by replacing the water that was lost.

The DI syndrome can therefore result from neurohypophyseal, nephrogenic, or primary polydipsic dysfunction (see Table 2). Neurohypophyseal DI is caused by partial or complete lack of ADH due to impairment of osmoreceptors or supraoptic nuclei. Nephrogenic DI results from congenital or acquired renal resistance to the endocrine effects of ADH. Primary polydipsic DI is caused by neurotic compulsive water drinking or by dysfunction of the thirst center as a consequence of hypothalamic disease.

**Diagnosis of Diabetes Insipidus**

The diagnostic approach to a patient with a suggestive clinical presentation consists of documenting the presence of DI, delineating its type, and identifying its cause. The diagnosis of DI and its type, in the absence of generally available reliable ADH assays, rests, at present, on the assessment of random serum and urine osmolalities, and on a provocative test that combines water deprivation and the administration of exogenous ADH. For practical purposes, other provocative tests are not needed. Once the type of DI is delineated, a search for its cause is undertaken (see Table 2).

**Random Serum and Urine Osmolalities.** A hyposmolar urine in the face of a hyperosmolar serum indicates impairment of water conservation due either to neurohypophyseal or nephrogenic DI. If administration of exogenous ADH leads to water conservation, the patient has neurohypophyseal DI. If no such response ensues, then the patient has nephrogenic DI.

A hypo-osmolar urine in the face of a hypo-osmolar serum in an untreated patient indicates primary polydypsia as the cause of the DI. The differentiation between neurotic water drinking and thirst-center dysfunction due to hypothalamic disease rests on ancillary evidence of psychiatric disorder or of organic hypothalamic disease.

A hypo-osmolar urine with a normal serum osmolality may result from any type of DI in which a compensated stage has been reached in water balance. In this situation, the differential diagnosis rests on provocative testing with water deprivation and exogenous ADH (see Appendix).

**Provocative Test.** The comparison of renal water conservation after water deprivation and after ADH administration provides a simple, reliable diagnostic test. Since normal individuals vary greatly in their maximum urinary concentrating capacities in the face of water deprivation, no absolute limits of normalcy can be defined. It is frequently difficult, therefore, to distinguish normalcy from an ADH deficiency state by assessing the absolute level of urinary osmolality reached after a period of dehydration. However, this differentiation is rendered possible by assessing the effects of exogenous ADH after water deprivation.
TABLE 2
Summary of approach to diabetes insipidus (DI) syndrome

**Etiology**
(a) Neurohypophyseal:
   1. Familial
   2. "Idiopathic"
   3. Organic hypothalamic disease: traumatic, inflammatory, degenerative, vascular, and neoplastic
(b) Nephrogenic:
   1. Congenital
   2. Acquired: e.g., chronic renal insufficiency, hypokalemia, hypercalcemia, sickle-cell disease, obstructive uropathy, drugs, e.g., lithium
(c) Primary polydipsic
   1. Psychiatric
   2. Hypothalamic disease

**Diagnosis**
(a) Does the patient have DI? And what is its type?

<table>
<thead>
<tr>
<th>Random urine and serum osmolalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypo-osmolar urine</td>
</tr>
<tr>
<td>Hypo-osmolar serum</td>
</tr>
<tr>
<td>Water deprivation test</td>
</tr>
<tr>
<td>Normal response</td>
</tr>
<tr>
<td>Primary polydipsic DI</td>
</tr>
<tr>
<td>Improved renal water conservation</td>
</tr>
<tr>
<td>Neurohypophyseal DI</td>
</tr>
<tr>
<td>Exogenous ADH test</td>
</tr>
<tr>
<td>No improvement in renal water</td>
</tr>
<tr>
<td>conservation</td>
</tr>
<tr>
<td>Nephrogenic DI*</td>
</tr>
</tbody>
</table>

(b) What is the cause of neurohypophyseal DI?
1. "Anatomical"
   - Noninvasive studies: skull x-rays, eye, visual fields, CT scanning
   - Invasive studies if indicated: pneumoencephalography, carotid angiography
2. "Functional"
   - Pituitary function tests
   - Basal hormone studies
   - Provocative tests if indicated

*Some patients with primary polydipsic DI and "renal medullary washout" have such a response. Their response reverts to normal after a few days of water restriction.

Primary polydipsic DI, where the patient has an essentially intact ADH-renal axis, the patient can concentrate urine maximally after water deprivation, and therefore exogenous ADH will not lead to further increase in urine concentration. A patient with neurohypophyseal DI cannot concentrate his urine maximally in the face of water deprivation, and exogenous ADH will lead to a distinct increase in his urine concentration ability. A patient with nephrogenic DI cannot concentrate his urine in the face of water deprivation and cannot respond to exogenous ADH by further increase.

The most difficult differential diagnosis is between partial neurohypophyseal DI and those cases of primary polydipsic DI where prolonged excessive water ingestion and diuresis have caused a "renal-medullary washout" (increased water diuresis impairs generation of the renal medullary hypertonicity, and thus water reabsorption by the distal nephron is reduced even in the face of a normal optimal ADH output). In each of these circumstances, the patient can concentrate his urine in the face of water deprivation, although suboptimally. At present, the differentiation is accomplished by the administration of exogenous ADH after water deprivation. A further rise in the urinary concentration ability will occur only with partial neurohypophyseal DI.

The following points relating to the diagnostic approach to DI should be stressed. 1) In neurohypophyseal and nephrogenic DI, thirst and increased water intake provide the body with the major compensatory mechanism to correct the negative water
balance. Impairment of consciousness or induced curtailment of water intake may rapidly lead to significant dehydration and hyperosmolality. 2) Cortisol, through its effect on glomerular filtration rate (GFR) and renal tubular function, is essential for the excretion of a water load. A patient with DI, who subsequently develops cortisol deficiency, may experience “amelioration” of his polyuria, thirst, and polydypsia. Therefore, a “spontaneous improvement” during the natural history of DI should prompt suspicion of cortisol deficiency. In such a situation, DI may again come to expression with replacement steroid therapy. Therefore, it is necessary to evaluate adrenocortical function, and institute replacement therapy if necessary, before testing for the existence of DI. 3) The diagnosis of “idiopathic” DI should not be made lightly. In some patients with this diagnosis, other manifestations of progressive organic hypothalamic disease may make their appearance in the course of follow-up review. Long-term follow-up study is, therefore, advisable for all patients with this diagnosis. 4) Since permanent DI results from some form of hypothalamic disease, it should not occur with “pure sellar” disease. A pituitary tumor would be able to cause DI only if it had significant suprasellar extension. 5) Diabetes insipidus that follows neurosurgical procedures in the hypothalamic pituitary area may either be a “transient” DI occurring any time during the first 1 to 4 days postoperatively and lasting 1 to 6 days with complete cure, or a “permanent” DI, or a “triphasic” DI. In the triphasic DI, there is first a transient DI generally lasting for a few hours to about 5 days; this is followed by a quiescent interphase and antidiuresis which lasts a few days and which finally leads to a permanent DI. It is generally agreed that the initial phase results from acute impairment of hypothalamic function, that the quiescent phase results from degeneration of supraoptic cells with release of stores of hormone, and that permanent DI results when such stores are depleted.

**Hypopituitarism**

Anterior pituitary failure may affect one of its hormones (isolated or monotropic failure) or more than one (multitropic failure), or all of the hormones produced by the gland (panhypopituitarism). In monotropic failure, any of the hormones may be lost. In multitropic or pantropic failure, hormone loss may occur concurrently or in any sequence. It is crucial to remember that, in the evolution of pituitary disease, progression from failure of one to more than one pituitary hormone may not occur at all, or may occur in a period of time extending over many years. In pantropic failure, hormone loss may occur in any sequence, but the usual loss is in this order: GH, LH and FSH, TSH, ACTH and PRL.

The endocrine manifestations of hypopituitarism are related to the hormonal deficiency and to the stage in life during which the deficiency makes its appearance. The composite clinical picture of hypopituitarism can therefore, be quite varied. In Table 3 is a list of the manifestations that should arouse suspicion of hypopituitarism. The diagnostic approach seeks to document the presence of hypopituitarism, to delineate the extent of hormonal loss, and to determine its cause.

**Diagnosis: Presence of Hypopituitarism**

Pituitary function can be assessed directly for all of its hormones by specific assays of circulating hormone level, or indirectly for its trophic hormones, by determination of the function of the target endocrine glands. In practice, the physician employs a combination of these approaches. It is obvious that a normal target gland function implies normal corresponding hypothalamic-pituitary endocrine function. However, an impaired target gland function may result from primary target gland failure, or it may be secondary to hypothalamic pituitary disease. If there is primary failure of a target gland, and, because of a decrease in negative feedback, the production of the appropriate tropic hormone is increased, and administration of exogenous tropic hormone will not stimulate such an impaired target gland. If, however, the failure of a target gland is secondary to hypothalamic pituitary disease, the production of the appropriate tropic hormone is decreased, and administration of exogenous tropic hormone can stimulate the atrophic target gland. Therefore, to determine whether a target gland failure is primary or is secondary to hypothalamic pituitary disease, one can measure the levels of the appropriate tropic hormone, when such assays are technically feasible, or conduct an exogenous tropic hormone-stimulation test when such assays are not so feasible.

**TSH-Thyroid Axis.** Serum total and free thyroxine (T4), and triiodothyronine (T3) can be measured by competitive protein binding (CPB) or radioimmunoassay (RIA). Serum TSH is measured by RIA.

In suspected hypothyroidism, one has to demonstrate low circulating thyroid hormone levels. Since serum T3 can be decreased in non-thyroid disease states (due to decreased peripheral deiodination of T4 to T3), one relies primarily on the assessment of T4: a total and a free serum thyroxine measurement or its equivalent (such as free thyroxine index, effective thyroid ratio). If hypothyroidism is documented, measurement of serum TSH is indicated: a high serum TSH indicates primary thyroid failure, whereas a low-normal or undetectable TSH levels indicate hypothalamic pituitary hypothyroidism.

**Gonadotropin-Gonadal Axis.** The pituitary gonadotropins may be measured by bioassay or by radioimmunoassay. The common bioassays of urinary gonadotropins measure the combined excretion of LH and FSH and cannot therefore give meaningful infor-
### TABLE 3

**Approach to hypopituitarism**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic</td>
<td>Drugs: Neuropharmacological</td>
</tr>
<tr>
<td>Congenital</td>
<td>Hormones</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Systemic disease</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Endocrinopathies: Thyroid disorders</td>
</tr>
<tr>
<td>Degenerative</td>
<td>Adrenal disorders</td>
</tr>
<tr>
<td>Vascular</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Nutritional disorders</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>In Childhood &amp; Adolescence</th>
<th>In Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Shortness of stature ? Hypoglycemia</td>
<td>? Hypoglycemia</td>
</tr>
<tr>
<td>Prolactin</td>
<td>None</td>
<td>Failure of postpartum lactation</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>Failure of sexual maturation in adolescents</td>
<td>Failure of sex-steroid-dependent and gametogenic functions</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>Impairment of CNS development in infants and newborns</td>
<td>Slowing of mental, physical, and sexual functions</td>
</tr>
<tr>
<td></td>
<td>Shortness of stature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failure of sexual maturation in adolescents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slowing of mental and physical functions</td>
<td></td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Ill-health, anorexia, weight loss, gastrointestinal disturbances, weakness, orthostatic hypotension, hypoglycemia, inability to excrete a water load, pallor, inability to tan, and propensity to adrenocortical crisis</td>
<td></td>
</tr>
</tbody>
</table>

### Diagnosis

<table>
<thead>
<tr>
<th>(a) Which hormone(s) are deficient?</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone</td>
<td>Basal HGH, and stimulation test if necessary</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Basal PRL, and stimulation test if necessary</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Basal LH and FSH</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>Testosterone and semen analysis in males, estrogen in females; other tests as indicated</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>Provocative tests rarely needed</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>Total and free T4</td>
</tr>
<tr>
<td></td>
<td>Plasma cortisol, urinary 17-KGS, and KS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) What is the cause?</th>
<th>“Anatomical” studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Provocative test rarely needed</td>
</tr>
</tbody>
</table>

*For abbreviations see Table of Definitions.*
Stimulation tests for the hypothalamic pituitary gonadal axis are available. Clomiphene stimulates the whole axis, GnRH the pituitary level, and exogenous gonadotropins stimulate the gonadal level. If gonadal function tests prove the patient to be hypogonadal, assessment of serum gonadotropins is indicated. In a hypogonadal patient, high FSH and LH levels indicate primary gonadal failure, while low-normal or low levels indicate hypothalamic pituitary hypogonadism.

Stimulation tests for the hypothalamic pituitary gonadal axis are available. Clomiphene stimulates the whole axis, GnRH the pituitary level, and exogenous gonadotropins stimulate the gonadal level. These tests are, however, rarely required for diagnostic purposes in suspected hypogonadism.

The ACTH-Adrenal Axis. To document a normal hypothalamic pituitary adrenal axis, the physician has not only to demonstrate that the patient can produce adequate levels of cortisol for day-to-day normal living, but he has also to show that the patient can increase his cortisol production optimally during periods of stress.

Cortisol secretion is assessed generally by serum cortisol determination using CPB or RIA. Since plasma cortisol levels fluctuate widely due to the effect of circadian rhythm, episodic secretion of ACTH, and stress, another measure of cortisol secretion is usually used, namely, a urinary 24-hour measurement of cortisol metabolites (24-hour urinary ketogenic or 17-hydroxy steroids) or of urinary free cortisol. The adrenal sex steroid secretion is generally measured by a 24-hour urinary 17-ketosteroid determination. Serum ACTH assays are not generally available, and are not absolutely necessary for the diagnosis of ACTH deficiency.

If, in a given patient suspected of ACTH deficiency, cortisol parameters are high normal, one can presume the ACTH axis to be intact. If their levels are borderline low or low-normal, the axis may be normal or impaired. The differentiation is done by a provocative test: the insulin tolerance test or propranolol-glucagon test or oral metyrapone test (see Appendix). All these tests stimulate the pituitary-adrenal axis at the hypothalamic or suprahypothalamic levels. A normal response indicates a normal axis. An impaired response to an effective challenge indicates hypoaldosteronism, either primary in adrenal cortex or secondary to hypothalamic pituitary disease. This latter differentiation is done by an exogenous ACTH stimulation test (see Appendix). An absent response to ACTH stimulation indicates primary adrenocortical failure, while a delayed but eventually normal response indicates hypothalamic pituitary disease.

If the levels of cortisol parameters are distinctly and reliably low, the diagnosis of adrenocortical failure is presumed. In such cases it is hazardous to proceed with the provocative challenges that test the whole axis. The differentiation between primary and secondary adrenocortical failure, in these circumstances, rests on exogenous ACTH stimulation.

If reliable serum ACTH assays are available, a high serum ACTH level in the face of hypocortisolism indicates primary adrenocortical failure, while a low value in such circumstances indicates adrenocortical failure secondary to hypothalamic pituitary disease.

Growth Hormone Axis. Serum GH is measured by RIA. The sensitivity of the presently available RIA's is such that it is difficult to distinguish between "low-normal" and "hypopituitarism" levels. Thus, basal values in normal persons may fall into the hypopituitary range. Since GH secretion is normally episodic, blood sampling may happen to occur during a trough of a secretory burst, and thus gives low values of serum GH. Because of these considerations, it may be necessary to carry out standard provocative tests to determine the status of GH secretion.

If GH deficiency is suspected, one can obtain a random serum GH determination, or perform a screening test in which a blood sample is obtained 60 to 120 minutes after the onset of sleep, or 15 to 20 minutes after vigorous exercise, especially in children. A high serum GH can exclude the diagnosis of GH deficiency. If a normal or undetectable level is obtained, a stimulation test is always required to document the diagnosis. A number of provocative tests for the assessment of GH reserve are in common use. These include insulin hypoglycemia, propranolol-glucacon, L-dopa, and intravenous arginine (see Appendix). We use either of the first two of these tests since they enable us to assess ACTH reserve concomitantly with that of growth hormone. It is important to remember that normal subjects do not invariably respond to each of these stimuli. To establish an unequivocal diagnosis of GH deficiency, the physician needs to demonstrate that a given patient does not respond to at least two different provocative tests.

Prolactin Axis. Prolactin is measured by RIA. In the diagnosis of a prolactin deficiency state, a random serum PRL may be obtained. A high normal value would exclude PRL deficiency. Since normal subjects may have baseline values approaching the lower limit of the assay sensitivity, the diagnosis of PRL deficiency in a given patient with low values rests on the demonstration of failure to respond to
Endocrinology in hypothalamic-pituitary disease

provocative stimuli. Chlorpromazine⁵⁰ and TRH provocative tests⁵⁰ are available. We regard the TRH as the provocative agent of choice since its administration enables us to assess TSH as well as prolactin reserves (see Appendix).

The availability of releasing hormones has raised the possibility that their administration to a given patient with suspected hypothalamic-pituitary disease will enable the physician to delineate pituitary failure from that of the hypothalamus. In such a patient, a positive response to the administration of exogenous releasing hormone, would be interpreted as indicative of hypothalamic disease, and an absent or blunted response as indicative of pituitary disease. Practically, however, these provocative tests have not proved to be as helpful as expected, and at present the differentiation between pituitary and hypothalamic disease in the majority of patients cannot be made on the basis of laboratory tests alone. Such laboratory differentiation awaits the development and the availability of reliable assays for the hypothalamic regulatory hormones.

In the differential diagnosis of secondary (pituitary) from tertiary (hypothalamic) hypothyroidism, the TRH test may be of some help.⁵,²⁷,²⁸,⁶⁴,⁸⁴ (see Appendix). An absent TSH response to TRH is strong evidence of intrinsic pituitary disease. A normal response, however, can be obtained in some patients with pituitary hypothyroidism, and thus is not useful in the differential diagnosis.

The GnRH test⁶⁶,⁶⁸,⁷³ (see Appendix) is not useful in the differential diagnosis between secondary (pituitary) and tertiary (hypothalamic) hypogonadism. A normal response can be obtained in patients with pituitary hypogonadism, and an impaired response in patients with long-standing hypothalamic hypogonadism. The normal response in patients with pituitary disease signifies the presence of gonadotroph remnants that can respond to the presumably supraphysiological doses of GnRH. An impaired responsiveness in hypothalamic disease results from loss of sensitivity of the gonadotrophs because of deficient intrinsic GnRH; this loss of sensitivity can be restored by the repeated administration of exogenous GnRH.

Causes of Hypopituitarism

The causes of hypopituitarism are listed in Table 3. Anterior pituitary failure may result from intrinsic pituitary gland disease damaging the secretory cells, from hypothalamic disease damaging the hypothalamic-pituitary endocrine unit. For a detailed discussion of the causes, the reader is referred to standard endocrine or neurosurgical texts. It is important to stress that pituitary failure may result from organic as well as functional disease. Hypopituitarism in the latter category is usually reversible if the causative factor is removed. It is crucial to keep in mind these functional states, since awareness of their existence can greatly simplify diagnostic and therapeutic steps. Functional hypopituitarism may result from exogenous administration of target gland hormones, neuropharmacological agents, chronic or acute systemic disease, and nutritional disorders such as anorexia nervosa and the emotional deprivation syndrome.

At present, cases of monohormonal gonadotropic, thyrotropic, and adrenocorticotropic failure induced by treatment with the respective target gland hormone are by far the most common cause of hypopituitarism. Prolonged administration of glucocorticoids may cause ACTH failure for a period that may vary from a few weeks up to 1 year depending on the nature of the glucocorticoid given, its potency and dosage, its duration of action, and time of administration. Following cessation of chronic thyroid hormone administration, the suppressed but otherwise normal TSH axis may take up to between 2 and 3 months to recover. After discontinuation of oral contraceptive therapy, postcontraceptive amenorrhea may last from a few weeks up to a number of months. Neuropharmacological agents may cause hypotalamic pituitary endocrine dysfunction by modifying hypothalamic neurotransmitter synthesis, release, action, or degradation.

If the cause of hypopituitarism in a given patient cannot be found, it is labeled “idiopathic.” A significant number of cases of hypopituitarism characterized as idiopathic turn out to be caused by undetected pituitary tumors that appear during follow-up review. Prolonged and close follow-up study is therefore essential in all patients with the “idiopathic” pituitary failure.

Hypopituitarism may be familial or hereditary, in which case it is often monotropic and associated with other congenital anomalies, or may be due to pituitary tumor which is one component of multiple endocrine neoplasia (MEN) Type I.

It is important to remember that complications from hypopituitarism may relate either to those resulting from the causative lesion, for instance, pituitary tumor resulting in visual field defect, or to those from pituitary failure per se. Hypopituitarism renders the patient liable to various sorts of metabolic and endocrine crises due to water intoxication, hypoglycemia, disturbance of temperature regulation, and inordinate sensitivity to CNS depressants. These crises may be the presenting manifestations of hypopituitarism.

PITUITARY TUMORS

Diagnostic Approach to Pituitary Tumors

The clinical manifestations that should arouse the suspicion of the presence of a pituitary tumor are listed in Table 4.

The diagnostic approach⁴,¹⁴,⁴⁰ aims at providing answers to the following questions: 1) Are there sellar
TABLE 4
Clinical approach to pituitary tumors*

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Anatomic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Effects of &quot;superior&quot; extension</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve II, optic chiasm and tract dysfunction</td>
</tr>
<tr>
<td></td>
<td>Hypothalamus-CNS dysfunction</td>
</tr>
<tr>
<td></td>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>Effects of &quot;inferior&quot; extension</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngeal mass</td>
</tr>
<tr>
<td></td>
<td>CSF rhinorrhea</td>
</tr>
<tr>
<td></td>
<td>Effects of &quot;lateral&quot; extension</td>
</tr>
<tr>
<td></td>
<td>Cranial nerves III, IV, VI, and V dysfunction</td>
</tr>
<tr>
<td></td>
<td>CNS dysfunction</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
</tr>
<tr>
<td></td>
<td>Hypersecretory states</td>
</tr>
<tr>
<td></td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td></td>
<td>Multiple Endocrine Neoplasia Type I</td>
</tr>
<tr>
<td></td>
<td>Parathyroid</td>
</tr>
<tr>
<td></td>
<td>Endocrine Pancreas</td>
</tr>
</tbody>
</table>

Diagnosis

(a) Are there "anatomic" sellar effects?
   Standard skull x-ray films
   Sellar tomograms
(b) Is there evidence of "anatomic" extrasellar effects?
   Eye and visual field examinations
   CT scanning
   Contrast studies, if indicated
(c) Are there pituitary hormone dysfunction effects?
   Basal hormone assays
   Provocative tests, if indicated
(d) Are the clinical effects due to a pituitary tumor or other space-occupying lesion?
   CT scanning
   Contrast studies
   Pneumoencephalogram
   Carotid angiogram
(e) Are there evidences of MEN Type I?
   Parathyroid: Serum calcium
   Endocrine pancreatic tests as appropriate

*For abbreviations see Table of Definitions.

TABLE 5
Diagnostic approach to acromegaly*

<table>
<thead>
<tr>
<th>Does the patient have acromegaly?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Basal serum GH and GH during an oral GTT</td>
</tr>
<tr>
<td>What are the effects of the pituitary tumor?</td>
</tr>
<tr>
<td>(a) Anatomic</td>
</tr>
<tr>
<td>Skull X-ray films and sellar tomograms</td>
</tr>
<tr>
<td>Eye and visual field exams</td>
</tr>
<tr>
<td>CT scanning</td>
</tr>
<tr>
<td>(b) Functional</td>
</tr>
<tr>
<td>Basal pituitary hormone assays</td>
</tr>
<tr>
<td>Provocative tests, if needed</td>
</tr>
<tr>
<td>(c) Is there evidence of MEN Type I?</td>
</tr>
<tr>
<td>Parathyroid: Serum calcium</td>
</tr>
<tr>
<td>Endocrine pancreatic tests as appropriate</td>
</tr>
</tbody>
</table>

*For abbreviations see Table of Definitions.

and extrasellar effects of a space-occupying lesion in the hypothalamic-pituitary area? 2) Is there evidence of hypothalamic-pituitary endocrine dysfunction in the form of hyper- or hypopituitarism? 3) Are the sellar, extrasellar, and hormonal disturbances related to the presence of a pituitary tumor or to another pathological process in the hypothalamic-pituitary area? 4) If the patient does have a pituitary tumor, does he have other associated endocrinopathy of the multiple endocrine neoplasia (MEN) Type I (primary hyperparathyroidism and endocrine tumors of the pancreas)?

The answers to these diagnostic questions are provided by the history, the physical examination, and by anatomical and functional studies. The anatomical studies would include skull films, sellar tomograms, visual field testing, and computerized tomography (CT) scanning of the head. Frequently, the physician may also have to resort to the use of contrast studies in the form of carotid angiography and pneumoencephalography. The functional studies usually consist of the assessment of anterior pituitary and neurohypophyseal functions in the basal state and the performance of pituitary provocative tests as is deemed appropriate. It will also include, if necessary, the biochemical and hormonal evaluation of parathyroid and endocrine pancreatic functions.

Diagnosis of Acromegaly

Does the Patient have Acromegaly?

The diagnostic approach to acromegaly is summarized in Table 5. The great majority of patients with acromegaly have high basal serum GH, and few have serum GH in the normal range.

The clinical findings in fully developed acromegaly are characteristic, and a high serum GH confirms the diagnosis and serves as a baseline to judge the course and effects of therapy. In the clinically less flagrant cases, a basal serum GH may be of use, since a low or undetectable level of GH excludes active acromegaly; but a high-normal or high serum GH is not enough for diagnosis since serum GH varies widely in normal subjects, especially females, and thus one must resort to a challenge test, the oral glucose tolerance test (GTT). A normal individual would show suppression of his serum GH to very low, or undetectable levels, 1 to 2 hours following the ingestion of glucose. Such normal suppression is not seen in patients with active acromegaly whose GH responses may show either no suppression, some suppression but distinctly less than normal, or paradoxical increase in GH in the face of a glucose load. Only a very rare acromegalic patient has serum GH levels that overlap with those of a normal person after glucose challenge. In such a case reliance has to be placed on multiple sampling over a 24-hour period. The acromegalic patient will show marked spontaneous fluctuations in the GH levels throughout the day.
Endocrinology in hypothalamic-pituitary disease

Some acromegalic patients have aberrant responses to certain provocative stimuli. Unlike normal individuals, such patients may show increased GH secretion in response to TRH and GnRH, and decreased secretion in response to L-dopa and apomorphine. Documentation of such paradoxic responses is, however, not needed in the usual diagnostic approach.

Evidence of Pituitary Dysfunction

In addition to the disturbance in the growth hormone axis, acromegalic patients show other evidence of endocrine dysfunction. It is estimated that 5% to 10% of patients with acromegaly have associated hyperprolactinemia. This is usually related to the presence of a mixed somatotrophic-lactotrophic tumor, but rarely to concomitant separate somatotrophic and lactotrophic tumors. It may also be related to hypothalamic-stalk dysfunction resulting from suprasellar extension of the pituitary tumor causing acromegaly. Thyroid disorders are common in acromegaly. Benign nontoxic multinodular goiter is the most frequent disorder. Hyperthyroidism, when present, is usually due to associated toxic nodular goiter or, rarely, to associated Graves' disease. Very rarely, however, hyperthyroidism may result from excessive TSH produced by the pituitary tumor. It is obviously very important to check for evidence of hypopituitarism (see under Hypopituitarism, above).

Effects of Tumor and Manifestations of MEN Type I

It should be stressed that acromegaly has been noted in the past in patients with carcinoid tumors and this association was considered a reflection of multiple endocrine neoplasia (MEN) Type I. Recently, in such a clinical setting, evidence has been provided that the carcinoid tumor produced GH-like peptides or possibly GH-releasing substances. Knowledge of this association should prompt a search for carcinoid tumors in acromegalic patients and if such are found, present experience dictates that therapeutic attention to the carcinoid tumor be given first, since such surgical ablation may lead to remission of the acromegalic process.

Diagnosis of Prolactin-Producing Pituitary Tumors

It is estimated that such tumors constitute about 40% to 60% of all pituitary tumors. Hyperprolactinemia is the hallmark endocrine abnormality. It may be clinically silent. In the male, however, it may present with decreased libido and potency, oligospermia, infertility, and, rarely, with galactorrhea. There is general agreement that hyperprolactinemia per se does not result in gynecomastia. In the female, hyperprolactinemia may present with galactorrhea, ovulatory defects (such as anovulation or short luteal phase leading to infertility), various menstrual disorders, and hirsutism. These endocrine sequelae of hyperprolactinemia result from the effect of the prolactin on the hypothalamic-pituitary-gonadal axis and on adrenal androgen production.

Presence of Galactorrhea

Most men and 30% of women with hyperprolactinemia do not have galactorrhea (Table 6). Galactorrhea, if present, is of variable degree, from copious milky, spontaneous, bilateral secretion to small amounts of nipple discharge expressible only on

**TABLE 6**

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactorrhea</td>
</tr>
<tr>
<td>Gonadal dysfunction</td>
</tr>
<tr>
<td>Males: Impaired libido and potency</td>
</tr>
<tr>
<td>Oligospermia and infertility</td>
</tr>
<tr>
<td>Females: Menstrual abnormalities</td>
</tr>
<tr>
<td>Anovulation and infertility</td>
</tr>
<tr>
<td>Hirsutism</td>
</tr>
<tr>
<td>Gynecomastia in males (rare)</td>
</tr>
<tr>
<td>May be clinically silent</td>
</tr>
</tbody>
</table>

**Etiology**

1. Excessive PRL production by the anterior pituitary

   (a) Lack of PIF
   - Hypothalamic- or Stalk-disease
   - Organic diseases of diverse etiologies
   - Functional:
     - Drugs: Neuropharmacological drugs
     - Antidopaminergic drugs
   - Hormones
   - Thyroid disorders
   - Adrenocortical disorders
   - Chest wall lesions
   - Renal failure

(b) "Autonomous"
- Prolactin-producing pituitary tumors

2. Excessive production of PRL by extrapituitary tissues
- Bronchogenic carcinoma
- Hypernephroma

**Diagnosis**

1. Is galactorrhea present?
   - Sudan IV staining
2. Is hyperprolactinemia present?
   - Basal serum PRL
3. Is there primary thyroid disorder?
   - Total and free T4 and serum TSH
4. Is there other evidence of pituitary disease?
   - Basal hormone assays
   - Provocative tests, if indicated
5. Are there anatomic effects of space-occupying lesion in hypothalamic-pituitary area?
   - "Anatomical" tests
6. Does the patient have a prolactinoma?
   - Consider: Basal serum PRL
     - Skull x-ray films and sellar tomograms
     - Other evidence of pituitary dysfunction
     - PRL-provocative tests (rarely helpful)
     - Other evidence of MEN Type I

*For abbreviations see Table of Definitions.
manual pressure. Therefore, a negative history of galactorrhea does not rule out its presence, and the physician should diligently search for this finding. If the discharge from the breasts is milky, bilateral, copious, and spontaneous, there is no doubt about the diagnosis of galactorrhea. However, if small amounts of "milky" nipple discharge are only obtained on manual pressure from one or both breasts, the diagnosis of galactorrhea is not definite since some breast diseases, benign or malignant, have been associated with a non-galactorrheic discharge. In such circumstances we have found Sudan IV staining of a smear of breast discharge to be useful in such differential diagnosis, since a positive stain for fat indicates galactorrhea.

Presence of a Prolactinoma

Hyperprolactinemia/galactorrhea may be caused by a variety of disorders. These are basically related to two pathogenetic mechanisms. In the first, there is inappropriate secretion of prolactin by the anterior pituitary gland, and in the second, the inappropriate secretion is by ectopic extrapituitary tumors, such as bronchogenic carcinoma. In practice, almost all the cases are due to a pituitary abnormality. This may be related to autonomous prolactin production by pituitary tumor or to hypothalamic stalk disorders. It is known that prolactin is under tonic hypothalamic inhibition so any disease of the hypothalamus or disruption of the hypothalamic-hypophyseal connections may lead to hyperprolactinemia. Such hypothalamic stalk disorders may be "functional," relating to the use of many antidopaminergic drugs, oral contraceptives, thyroid disorders, adrenal disorders, renal failure, or irritative lesions of the chest wall, or they may be "organic" caused by traumatic, inflammatory, vascular, degenerative, or neoplastic diseases affecting the hypothalamus and stalk. Hyperprolactinemia has also been reported to be associated with a primary empty sella syndrome. In many cases the most careful evaluation, even including surgical exploration of the pituitary, fails to document an identifiable cause for the hyperprolactinemia/galactorrhea, and such states are labeled as "idiopathic." It is important to stress that careful long-term follow-up review of such "idiopathic" cases is necessary, since an identifiable lesion may make itself known at some stage during a long-term follow-up period.

It can be seen, then, that a good history, general examination, and selective laboratory and radiological tests can exclude most of the causes listed above. In the remainder, the main diagnostic question is whether or not a prolactin-producing pituitary tumor is present.

At present, the diagnosis of prolactinomas is based on composite assessment of serum prolactin, skull films, and sellar tomography, presence of evidence of other pituitary dysfunction, and occasionally on the use of certain PRL-provocative tests. In a hyperprolactinemic patient, the level of serum PRL is directly correlated with the likelihood of a tumor. It is generally agreed that a serum prolactin greater than 250 ng/ml is almost always due to a tumor. It is important to stress, however, that a serum prolactin below 250 ng/ml does not exclude the presence of a prolactinoma. Evidence of a space-occupying lesion in the sella on skull films or on sellar tomograms constitutes solid grounds for the provisional diagnosis of prolactinoma. The presence of multiple anterior pituitary hormone deficiencies also makes the diagnosis extremely likely.

Certain pharmacological provocative tests are available for the PRL axis, and these include stimulation by TRH or chlorpromazine, and suppression by L-dopa or bromocryptine. It was originally hoped that such provocative tests would help in the differential diagnosis of hyperprolactinemia. Those cases due to a prolactinoma, a supposedly autonomous state, were expected to show blunted responsiveness to these provocative agents, while other nonautonomous causes would show appropriate responses. However, in practice, these tests have not been found helpful in the differential diagnosis, since only a minority of patients with prolactinomas do show the characteristic blunted responses.

Diagnosis of Cushing's Syndrome

Cushing's syndrome consists of a constellation of signs and symptoms resulting from the exposure of tissues to excess cortisol. It may be caused by chronic administration of supraphysiological doses of cortisol or its glucocorticoid analogues (exogenous Cushing's syndrome), or by excessive cortisol production by adrenocortical tissue within the body (endogenous Cushing's syndrome). The latter, in turn, may be caused by excessive production of cortisol from an autonomous adrenocortical cause (adrenal adenoma or carcinoma), or from hyperplastic adrenocortical tissue in response to exposure to excess trophic hormone, ACTH. This excess ACTH may be produced by anterior pituitary abnormality (Cushing's syndrome) or by a non-endocrine tissue tumor (ectopic ACTH syndrome).

The diagnostic laboratory approach to Cushing's syndrome (Table 7) consists of two parts: first, the documentation of the presence of Cushing's syndrome, and second, the identification of its cause. In addition, as dictated by these laboratory tests, "anatomical studies" of the hypothalamic-pituitary area or adrenal areas, or sites of ectopic ACTH production are used to delineate tumors in these areas which cause the Cushing's syndrome. The common laboratory tests that are used in the assessment of hypercortisolinemia are serum cortisol, urinary ketogenic or 17-hydroxysteroids, urinary 17-ketosteroids, and urinary free cortisol. It is important
Endocrinology in hypothalamic-pituitary disease

TABLE 7
Approach to Cushing's syndrome*

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cushing's Disease</th>
<th>Adrenal Tumors</th>
<th>Ectopic-ACTH syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) &quot;ACTH-dependent&quot;</td>
<td>Serum ACTH</td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>Cushing's disease</td>
<td></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>Ectopic ACTH tumor</td>
<td></td>
<td>normal or high</td>
<td>undetectable</td>
</tr>
<tr>
<td>Exogenous ACTH</td>
<td></td>
<td>pituitary</td>
<td>adrenal</td>
</tr>
<tr>
<td>(b) &quot;Non-ACTH-dependent&quot;</td>
<td>Metapyrone stimulation</td>
<td>absent</td>
<td>high</td>
</tr>
<tr>
<td>Adrenal tumors</td>
<td></td>
<td></td>
<td>ectopic site</td>
</tr>
<tr>
<td>Bilateral nodular hyperplasia</td>
<td>Serum ACTH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exogenous glucocorticoid</td>
<td>Anatomical studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis
(a) Is Cushing's syndrome present?
- Short dexamethasone-suppression test
- Low-dose dexamethasone-suppression test
(b) What is the cause?
- High-dose dexamethasone-suppression test
- Metapyrone stimulation test
- Serum ACTH
- Anatomical studies

Table:  
- Cushing's Disease: present
- Adrenal Tumors: absent
- Ectopic-ACTH syndrome: absent

<table>
<thead>
<tr>
<th>Test</th>
<th>Cushing's Disease</th>
<th>Adrenal Tumors</th>
<th>Ectopic-ACTH syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>high-dose dexamethasone suppression test</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>metapyrone stimulation</td>
<td>present</td>
<td>absent</td>
<td>high</td>
</tr>
<tr>
<td>serum ACTH</td>
<td>normal or high</td>
<td>undetectable</td>
<td>ectopic site</td>
</tr>
<tr>
<td>anatomical studies</td>
<td>pituitary</td>
<td>adrenal</td>
<td></td>
</tr>
</tbody>
</table>

* Dex = dexamethasone; for other abbreviations see Table of Definitions.

that a physician keep in mind the extra-adrenal factors that may affect these measurements of cortisol secretion. Serum cortisol levels are influenced by the levels of cortisol-binding-globulin, the episodic secretory burst of ACTH, and the influence of stress on the axis. The urinary 17-ketogenic or 17-hydroxysteroids are influenced by hepatic and renal function, body weight, thyroid function, and accuracy of the 24-hour urine collection. The urinary free cortisol is considered as the best single test for the diagnosis of hypercortisolism, but its levels are also influenced by the GFR and the accuracy of a 24-hour urine collection. These considerations should lead to the conclusion that no available single laboratory parameter can be totally reliable in the diagnosis of Cushing's syndrome. For such a diagnosis, the physician has to resort to testing the normalcy of the homeostatic function of the hypothalamic pituitary adrenal axis.

Does the patient in fact have Cushing's syndrome? Whereas the normal hypothalamic pituitary adrenal axis is suppressed by supraphysiological circulating levels of cortisol or its glucocorticoid analogues, the impaired axis in Cushing's syndrome is resistant to such suppression. This principle forms the basis of the so-called "short" and "low-dose" dexamethasone-suppression test (see Appendix). Normal suppression following the "short overnight dexamethasone suppression test" excludes for practical purposes the diagnosis of Cushing's syndrome. Failure of suppression, however, is not diagnostic of Cushing's syndrome since some normal but stressed individuals may fail to suppress. One then resorts to the "low-dose dexamethasone suppression test." Failure of suppression of cortisol secretion parameters during the "low-dose" test establishes for practical purposes the diagnosis of Cushing's syndrome.

What is the cause of Cushing's syndrome? Endogenous Cushing's syndrome may be divided into ACTH-dependent type (Cushing's syndrome and ectopic ACTH tumor) and non-ACTH dependent type (adrenal adenoma or carcinoma). It is only in Cushing's disease that the CRF-ACTH unit retains some of its homeostatic responses to the circulating levels of cortisol or its glucocorticoid analogue, since it will always be stimulated by a decrease in circulating cortisol and will be suppressed by markedly supraphysiological levels of circulating cortisol. With this in mind, it can be seen that the differential diagnosis of Cushing's syndrome rests on the determination of serum ACTH when this is available, and the conduct of high-dose dexamethasone-suppression test and metapyrone stimulation test (see Appendix). In Cushing's disease, serum ACTH is high-normal or high, the majority of patients show significant suppression during high-dose dexamethasone-suppression test, and almost all show positive responses to metapyrone stimulation test. Cushing's syndrome induced by an ectopic ACTH-producing tumor is resistant to these pharmacological manipulations, and the patient has usually very high levels of circulating ACTH. Patients with adrenal tumors are also resistant to pharmacological manipulations, but their serum ACTH levels are undetectable due to the sup-
TABLE 8

Approach to inappropriate antidiuretic hormone syndrome*

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypothalamic</td>
</tr>
<tr>
<td>(a) Organic CNS disease</td>
</tr>
<tr>
<td>(b) Metabolic diseases:</td>
</tr>
<tr>
<td>e.g., hypothyroidism, intermittent porphyria</td>
</tr>
<tr>
<td>(c) &quot;Faulty&quot; signals from volume receptors:</td>
</tr>
<tr>
<td>e.g., mitral commissurotomy</td>
</tr>
<tr>
<td>(d) Drugs:</td>
</tr>
<tr>
<td>ADH</td>
</tr>
<tr>
<td>Narcotics</td>
</tr>
<tr>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Thiazides</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Clodibrate</td>
</tr>
<tr>
<td>Vincristine</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>2. &quot;Extrahypothalamic&quot;</td>
</tr>
<tr>
<td>(a) Malignant tumors: lung, pancreas, duodenum, etc.</td>
</tr>
<tr>
<td>(b) Pulmonary inflammatory states:</td>
</tr>
<tr>
<td>e.g., pneumonia, abscess, tuberculosis</td>
</tr>
</tbody>
</table>

Clinical Manifestations
Weight gain in absence of edema
Anorexia, nausea, vomiting
CNS dysfunction

Diagnosis
1. Is SIADH present?
   - serum hypo-osmolality-hyponatremia
   - inappropriately hyperosmolar urine
   - excessive renal sodium excretion
   - absence of volume depletion or ECF sequestration
   - absence of adrenal or renal dysfunction
2. What is its cause?
   - Studies as appropriate

*For abbreviations see Table of Definitions.

Inappropriate ADH Syndrome

The secretion of ADH is "appropriate" in terms of homeostatic needs if it occurs in response to plasma hyperosmolality or to hypovolemia. When persistent secretion occurs in the absence of these stimuli it leads to clinical manifestations grouped together under the label of "syndrome of inappropriate antidiuretic hormone" (SIADH).44-46

Etiology

Basically, the possible causes of SIADH include an inappropriate excessive secretion of ADH from the hypothalamus or from extrahypothalamic tissues capable of such endocrine function (Table 8).

A hypothalamic source may result from impairment of hypothalamic function due to CNS or systemic disease, from the use of certain drugs,44 which enhance ADH secretion or its effects on the distal nephron, and from bombardment of the neurohypophyseal nuclei from "faulty signals" that originate from volume receptors. An extrahypothalamic source of inappropriate ADH secretion occurs in certain neoplastic and inflammatory states of nonendocrine tissues, particularly the lung.

Pathophysiology

Persistent secretion of ADH, in the face of continued water intake, will lead to enhanced water conservation by the distal nephron, positive water balance in all body-fluid compartments, expanded blood volume and hypo-osmolarity of the body fluids, and hyponatremia. The urine which is elaborated is hyperosmolar relative to the plasma hypo-osmolality.

As a result of the expanded blood volume, the GFR is increased and the renin-angiotensin-aldosterone mechanism is suppressed. These responses, together with renal hemodynamic adjustments, the so-called "third factor," lead to enhanced renal salt wastage.

Such an adjustment will prevent further extracellular fluid (ECF) volume expansion, and thus edema will not occur. It will enable patients with SIADH to excrete a salt load promptly, and thus have their urinary sodium closely paralleling their dietary sodium intake.

It should be noted that for the full syndrome to develop, there has to be continued water intake in the face of persistent secretion of ADH. Restriction of water intake, voluntary or induced, will prevent the syndrome from developing, or, if the syndrome is already present, it will lead to amelioration of the abnormalities. Attention is drawn also to the fact that the homeostatic adjustments in SIADH can protect the body against volume expansion but cannot prevent progressive hypo-osmolality of the body fluids and hyponatremia if water intake remains unchecked.

Diagnosis

For the prompt excretion of a water load, a person needs a normal hypothalamic function, which responds to the water load by the suppression of secretion of ADH, and normal cardiocirculatory and renal functions. A normal cortisol state is needed for adequate suppression of ADH secretion and for normal renal water excretion. For suppression of ADH secretion in the face of a water load the person should not be hypovolemic, since the volume depletion stimulus for ADH secretion will override the suppressive effect of hypo-osmolality induced by the water load.

Therefore, inability to excrete a water load can result from SIADH, hypovolemia, heart failure, sequestration of ECF on the venous side of the circulation, as in ascites and the nephrotic syndrome, and from renal or adrenocortical failure.

The clinical features that should raise the suspicion of SIADH are weight gain in the absence of edema, and CNS dysfunction. Routine laboratory studies usually show a reduced blood urea nitrogen (BUN), serum uric acid, and serum creatinine (due to the in-
creased GFR), hyponatremia with a urinary sodium greater than 20 mEq/liter, and an inappropriately hyperosmolar urine in the face of serum hypo-osmolarity. If serum assays of ADH are available, serum ADH will be detectable in the face of serum hypo-osmolarity. The diagnosis of SIADH is confirmed by the exclusion of the other causes of abnormalities of water balance mentioned above.

APPENDIX

Some Commonly Used Pituitary Provocative Tests

**Water Deprivation Test**

**Objective.** To determine the presence and cause of the diabetes insipidus (DI) syndrome.

**Procedure.** Patients with significant polyuria should only be deprived of fluid from 8:00 a.m. on the morning of the test. Those with mild polyuria can be deprived from 8:00 p.m. the evening before the test. The patient should be weighed at the start of the test and at 2 to 3 hourly intervals thereafter, and the test should be terminated if the patient loses more than 5% of body weight. Aliquots of urine for osmolality should be collected at the start of the dehydration and then, beginning at 8:00 a.m. on the day of the test, at hourly intervals. When the urine osmolality becomes constant with a change of less than 30 mOsm/kg between two consecutive hourly collection periods, 5 units of aqueous vasopressin is injected subcutaneously. Urine for osmolality is collected again 60 minutes postinjection and the test is terminated. Blood sample is collected for serum electrolytes and osmolality at the start of the dehydration period and just before the administration of ADH. If there is any question about the patient's reliability in insuring water deprivation, he or she should be observed throughout the test period.

**Interpretation.** In a normal individual, the urine osmolality plateaus about 600 mOsm/kg or above, and does not increase more than an additional 5% after the injection of ADH. A patient with suspected DI who can respond in this fashion must have primary polydipsic DI. A patient who fails to show a significant rise in urine osmolality after water deprivation, but whose urinary osmolality rises more than 9% after ADH administration, must have neurohypophyseal DI. A patient whose urine osmolalities do not reach 600 mOsm/kg or above after water deprivation, and do not increase more than 5% after administration of ADH must have a renal defect in responsiveness to ADH. This may be due to nephrogenic DI or to the renal wash-out effect of primary polydipsic DI. These two are distinguished by reducing excess water intake for several days. Such a maneuver would reconstitute the renal medullary hypertonicity in primary polydipsic patients and therefore, on repeat water deprivation and ADH administration test, their responses will be normalized. No such normalization occurs in nephrogenic DI.

**Insulin Hypoglycemia Test**

**Objective.** The stress of hypoglycemia results in secretion of a number of hormones: GH, ACTH and cortisol, catecholamines, and prolactin. This is a standard test for the assessment of GH and ACTH reserves.

**Procedure.** The test is performed after an overnight fast. Regular insulin is given intravenously at a dosage of 0.15 units/kg body weight, and blood samples for plasma glucose, serum GH, and plasma cortisol are obtained at 0 minutes and at half-hourly intervals for 2 hours following administration of insulin. Patients who are suspected of being insulin resistant, for instance, those with obesity, Cushing's syndrome, or acromegaly, will frequently need 0.15 to 0.3 units/kg of insulin. Patients who are suspected of having hypopituitarism should receive 0.05 units/kg of regular insulin initially. For effective GH challenge, there should be at least a 50% drop in plasma glucose. For effective ACTH challenge, there should be clinically evident manifestations of stress in the form of perspiration, tachycardia, and apprehension that result from hypoglycemia. If such criteria are not observed 45 minutes to 1 hour after the administration of insulin, a repeat dose can be given. A medical attendant should be present throughout the test. Fifty percent glucose should be available for intravenous administration and should be promptly given if serious manifestations of hypoglycemia like significant impairment of consciousness, convulsions, or chest pain develop. The test is hazardous in patients with severe documented panhypopituitarism or in elderly patients. It is contraindicated in the presence of convulsive disorder, or ischemic cardiovascular or cerebrovascular disease.

**Interpretation.** Serum GH should increase more than 5 ng/ml or to a level greater than 10 ng/ml. Some normal individuals do not show this response and GH deficiency will be documented only if there is failure to respond to more than one provocative agent. Plasma cortisol levels should rise to a maximum of over 20 μg% or by at least 7 μg%.

**Propranolol-Glucagon Provocative Test**

**Objective.** Glucagon stimulates GH and ACTH secretion by a mechanism that is presently undetermined. This stimulatory effect of glucagon is augmented by propranolol, which blocks the beta-catecholaminergic receptors in the hypothalamic pituitary area.

**Procedure.** The patient should fast from midnight. At 7:00 a.m., propranolol is given in a dose of 40 mg orally. Baseline serum GH and cortisol are obtained at 9:00 a.m. and 1 mg of glucagon is administered intramuscularly. Repeat sampling is done at 11:00 a.m. and 12:00 noon. Nausea, vomiting, apprehension, and hypoglycemia may occur from glucagon administration, but these side effects are usually mild and transient. The test is contraindicated in patients with heart disease or bronchial asthma and is avoided in diabetes mellitus because it may be unreliable or risky.

**Interpretation.** See under insulin hypoglycemia test.

**L-dopa Test**

**Objective.** Dopaminergic mechanisms play an important role in GH and PRL secretion. Increased dopaminergic activity causes stimulation of GH secretion and suppression of secretion of prolactin. L-dopa can cross the blood-brain barrier and exert a dopaminergic effect on hypothalamic pituitary DA receptors. The L-dopa test is used to assess GH reserve and to test suppressibility of prolactin secretion.

**Procedure.** The patient should be fasting from midnight and at rest. Blood samples are obtained for serum GH and prolactin determination and L-dopa is given orally in a dose of 500 mg to an adult or a dose of 10 mg/kg for children. Repeated sampling is done at 1, 2, and 3 hours following the administration of L-dopa. If the prolactin levels are being
measured, it is best to perform this test late in the morning so that the diurnal fall in prolactin would have already occurred before the start of the test. This test is well tolerated; less than half the patients suffer transient nausea or vomiting.

Interpretation. Criteria for a GH reserve are as those outlined under insulin hypoglycemia test. A normal suppressibility of prolactin is that which reduces serum prolactin levels by greater than 50%.

**Thyrotropin-Releasing Hormone Test**

Objective. Assessment of the status of TSH and prolactin secretion.

Procedure. The patient should be fasting from midnight and at rest. A blood sample is obtained for basal serum TSH and PRL determination. 500 μg of TRH are administered intravenously as a bolus and repeated sampling is done at 30 and 60 minutes after administration. More than half of the subjects experience transient nausea, facial flushing, urge to urinate, peculiar taste in the mouth, and chest tightness. No serious side effects have been reported and there are no known contraindications.

Interpretation. The responses in the normal individual vary with age, sex, level of basal serum TSH, and prolactin among other factors. Each laboratory should standardize its normal responses. The TRH test is useful in the diagnosis of primary thyroid disorders. A normal response almost completely excludes the diagnosis of thyrotoxicosis. In primary hypothyroidism, basal serum TSH levels are increased and the response to TRH is exaggerated and prolonged. Blunted responses can be seen in thyroid disorders that are autonomous and not TSH-dependent. For the utility of this test in hypothalamic pituitary disease, see the text of the article.

**Gonadotropin-Releasing Hormone Test**

Objective. This test is useful in the assessment of gonadotropic function reserve.

Procedure. With the patient at rest, blood samples for serum LH and FSH are taken at 0, 30, and 60 minutes after the administration of GnRH. For routine testing of pituitary gonadotropic reserve, GnRH is given in the dose of 100 μg as an intravenous bolus. There are no known side effects or contraindications.

Interpretation. Normal responses vary widely depending on a host of factors among which are age, sex, and phase of the menstrual cycle in adult women in their reproductive years. Each laboratory should standardize its normal responses. In primary gonadal failure the GnRH responses are generally exaggerated and prolonged. For its use in hypothalamic pituitary disease, refer to the article text.

**Rapid Screening Dexamethasone-Suppression Test**

Objective. Dexamethasone is a potent glucocorticoid which suppresses ACTH secretion through negative feedback effect on the hypothalamus and pituitary. It is given in small quantities and it is not measured by routine laboratory tests used for the measurement of cortisol and its metabolites. The rapid screening test is used in screening patients with suspected Cushing's syndrome.

Procedure. Plasma cortisol is determined at 8:00 a.m. Dexamethasone, 1 mg, is given orally at 11:00 p.m., and another plasma cortisol determination is done on the following morning at 8:00 a.m. This test is without complications.

Interpretation. Serum cortisol is generally 5 μg% or less in the morning following dexamethasone administration in normal individuals. A patient with Cushing's syndrome would have a serum cortisol above 10 μg%. This test is abnormal in 97% of patients with proved Cushing's syndrome. False-positive results may occur in acutely ill or stressed individuals and in patients on estrogen therapy or on drugs that are known to modify hepatic microsomal degradative enzymes, such as Dilantin. Patients who show lack of suppression should undergo further evaluation with a standard low-dose (2 mg) dexamethasone-suppression test.

**Dexamethasone-Suppression Test**

Objective. To diagnose Cushing's syndrome and to attempt to determine its cause.

Procedure. Dexamethasone should be administered every 6 hours in the following manner. During the "low-dose" dexamethasone-suppression test, it is given in the dose of 0.5 mg every 6 hours for 48 hours, and this is immediately followed by the "high-dose" dexamethasone-suppression test during which 2.0 mg is given every 6 hours for 48 hours. Daily 24-hour urine collection for urinary free cortisol, ketogenic and ketosteroid and urinary creatinine, and plasma cortisol determinations are carried out for at least 2 days before and daily during the entire period of dexamethasone administration. This is a safe test, essentially free of side effects.

Interpretation. Normal individuals will suppress their ACTH-adrenal axis in response to the low-dose dexamethasone suppression test. This will be reflected in serum cortisol values of less than 5 μg%, urinary ketogenic steroids less than 5 mg/24 hr, and urinary free cortisol less than 20 μg/24 hrs. Patients with Cushing's syndrome fail to show such suppression. It should be noted that severely stressed individuals without endocrine disease may fail to suppress on the low dose.

In response to the high-dose dexamethasone-suppression test, the majority of patients with pituitary-dependent Cushing's disease will suppress their cortisol secretion parameters greater than 50% of their baseline, whereas patients with Cushing's syndrome due to an adrenal tumor or ectopic ACTH syndrome do not show this degree of suppression.

**Metapyrone-Stimulation Test**

Objective. Metapyrone inhibits 11-beta-hydroxylase, the enzyme that catalyzes the final step in cortisol biosynthesis. A decrease in cortisol secretion results which reduces the negative feedback effects on ACTH and leads to a compensatory rise in ACTH secretion which in turn stimulates increased steroid biosynthesis and an increase in secretion of the cortisol precursor, 11-deoxycortisol or compound S. The level of 11-deoxycortisol can be measured indirectly as urinary 17-ketogenic steroids or 17-hydroxysteroid or more specifically by radioimmunoassay in the urine or plasma. The metapyrone stimulation test is useful in two clinical circumstances: in the assessment of ACTH reserve, and in the differential diagnosis of Cushing's syndrome.

Procedure. In patients suspected of having decreased ACTH reserve and in those with Cushing's syndrome related to an adrenal tumor, metapyrone may cause a significant decrease in cortisol secretion and lead to the development of an adrenocortical crisis. Therefore, the
Endocrinology in hypothalamic-pituitary disease

The metapyrone test should be done only on hospitalized patients and under close medical supervision. Metapyrone is given in a dosage of 500 mg every 4 hours for six doses. Twenty-four-hour urine collection for 17-ketogenic steroids and creatine, and blood samples for serum cortisol and serum compound S are drawn daily for the day preceding, the day of, and the day following metapyrone administration (metapyrone dose for children is 300 mg/m square body surface area/dose).

Interpretation. A normal individual would have stimulation of his pituitary adrenal axis in response to metapyrone. This would be reflected by an increase in urinary ketogenic steroids to 2-4 times the basal value and by an increase in his serum compound S to greater than 10.5 µg%. A patient with adrenocortical failure, whether primary or secondary, would have an impaired response.

In the differential diagnosis of Cushing’s syndrome, patients with Cushing’s disease are hyper-responsive to metapyrone stimulation. In those patients with Cushing’s syndrome relating to the presence of an adrenal tumor, or ectopic ACTH-producing tumor, there would be either no change or a decrease in the parameters of cortisol secretion.

### Rapid ACTH (Cortrosyn) Test

**Objective.** Cortrosyn is a synthetic 1-24 ACTH compound. This test is used as a screening test for adrenocortical function.

**Procedure.** A serum cortisol is obtained and 250 µg of cortrosyn are injected intravenously as a bolus; further blood samples for serum cortisol are obtained at 30 and again at 60 minutes after cortrosyn administration. This test is essentially free of side effects.

**Interpretation.** Normal individuals exhibit a rise in serum cortisol of more than 7 µg% or to a level of greater than 20 µg%. Such a response excludes the diagnosis of adrenal insufficiency. Failure of such rise may be due to adrenocortical failure, while patients with secondary adrenocortical disease, or secondary, due to hypothalamic pituitary disease. In such cases, a standard ACTH stimulation test should be undertaken.

### Standard ACTH-Stimulation Test

**Objective.** This is a test of adrenocortical function and is used in the differential diagnosis between primary and secondary adrenocortical failure.

**Procedure.** There are several techniques for testing adrenocortical responsiveness to ACTH. One can administer long-acting ACTH (acthar gel) in a dose of 40 units intramuscularly twice a day for 3 to 5 days, or one can infuse crystalline ACTH for 8 hours on 3 consecutive days. Cortisol parameters to be followed are serum cortisol, urinary 17-ketogenic or hydroxysteroids, and urinary free cortisol and creatinine. These are followed for 2 days before and daily during the ACTH administration. During the ACTH-stimulation test, the patient is covered with dexamethasone, 0.5 mg orally twice a day, because anaphylactic reactions have occurred rarely in some patients during the test.

**Interpretation.** With ACTH stimulation the serum cortisol normally rises to 50 µg% and urinary cortisol parameters to 2 to 4 times the baseline values. Patients with primary adrenocortical deficiency fail to demonstrate such a response, while patients with secondary adrenocortical failure show a sluggish or delayed but eventually normal response.

### References

evaluation of prolactin secretion: a guide to therapy. 
J Clin Invest 51:706-709, 1972

24:251-270, 1973

21:241-283, 1965


45:429-436, 1966

1:115-125, 1972

290:886-890, 1974

36:1069-1073, 1973

32:470-475, 1971

33:873-876, 1971

296:589-600, 1977

32. Landon J, Greenwood FC, Stamp TCB, et al: The plasma sugar, free fatty acid, cortisol, and growth hormone response to insulin. II. In patients with hypothalamic or pituitary dysfunction or anorexia nervosa. J Clin Invest
45:437-449, 1966

33. Liddle GW: Test of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab
20:1539-1560, 1960

19:875-894, 1959

35. Liddle GW, Island D, Meador CK: Normal and abnormal regulation of corticotropin secretion in man. Recent Prog Horm Res
18:125-166, 1962

80:464-469, 1974


74:471-480, 1971

285:725-739, 1971

73:721-729, 1970

10:99-103, 1976

32:470-475, 1971


4:73-77, 1973

12(7):37-44, 1977

49. Moses AM, Miller M, Streten DHP: Pathophysiologic and pharmacologic alterations in the release and action of ADH. Metabolism
25:697-721, 1976

133:459-463, 1974

2:190-191, 1971


86:243-250, 1977

54. Pavlatos FC, Smilo RP, Forsham PH: A rapid screening test for Cushing's syndrome. JAMA
193:720-723, 1965


20:1614-1621, 1960


52:2340-2352, 1973

59. Robinson AG, Frantz AG: Radiiodimunooassay of posterior pituitary peptides: a review. Metabolism
22:1047-1057, 1973

73:49-54, 1970

140:987-988, 1963
Endocrinology in hypothalamic-pituitary disease


Address reprint requests to: Charles F. Abboud, M.D., Consultant, Endocrinology/Metabolism and Internal Medicine, Mayo Clinic, Rochester, Minnesota 55901.