Management of Endocrine Disorders

JEROME M. HERSHMAN

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JEROME M. HERSHMAN, M.D.

Professor of Medicine,
UCLA School of Medicine,
Chief, Endocrinology Section,
Medical Service,
Wadsworth Veterans Administration Hospital,
Los Angeles, California

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Preface

This practical book has as its aim to give the reader a thorough understanding of the diagnosis and therapy of the most common endocrine disorders. Each chapter describes the principal clinical features of various endocrine diseases and presents the diagnostic tests which are most useful in 1980. Each chapter also gives the essential details of therapy for the management of specific diseases. To emphasize practical management, each chapter contains several case studies with an analysis of the diagnosis and therapy of that patient. Selected references are included for the interested reader. The authors state the rationale for their practice and also cite controversial issues and unresolved problems.

The volume is written for general internists and family physicians. Residents in internal medicine and family practice should also find it useful. For medical students and practitioners who wish to review the basic pathophysiology of endocrine disorders, I have written a companion volume, *Endocrine Pathophysiology: A Patient Oriented Approach*, also published by Lea & Febiger (1977, 358 pages).

The present volume is a complete guide to the practical aspects of clinical endocrinology.

JEROME M. HERSHMAN

Contributors

GLENN D. BRAUNSTEIN, M.D.
Associate Professor of Medicine,
UCLA School of Medicine,
Director, Division of Endocrinology,
Cedars-Sinai Medical Center,
Los Angeles, California

HAROLD E. CARLSON, M.D.
Associate Professor of Medicine,
UCLA School of Medicine,
Assistant Chief, Endocrinology
Wadsworth VA Hospital
Los Angeles, California

ERNEST J. DRENICK, M.D.
Professor of Medicine,
UCLA School of Medicine,
Chief, General Medicine,
Wadsworth VA Hospital,
Los Angeles, California

ALAN A. FOGELMAN, M.D.
Associate Professor of Medicine
and Chief, Division of Cardiology,
UCLA School of Medicine,
Los Angeles, California

JEROME M. HERSHMAN, M.D.
Professor of Medicine,
UCLA School of Medicine,
Chief, Endocrinology Section,
Medical Service,
Wadsworth VA Hospital
Los Angeles, California

SEYMOUR R. LEVIN, M.D.
Associate Professor of Medicine,
UCLA School of Medicine,
Chief, Special Diagnostic and
Treatment Unit,
Director, Diabetes Clinic,
Wadsworth VA Hospital,
Los Angeles, California

FREDERICK R. SINGER, M.D.
Professor of Medicine and
Orthopaedic Surgery,
University of Southern California
School of Medicine,
Associate Director, USPHS
Clinical Research Center,
LAC/USC Medical Center,
Director, Endocrine Laboratory,
Orthopaedic Hospital/USC Bone
and Connective Tissue Laboratories,
Los Angeles, California

REBECCA Z. SOKOL
Fellow, Division of Endocrinology,
Harbor-UCLA Medical Center,
Torrance, California

RONALD S. SWERDLOFF, M.D.
Professor of Medicine
UCLA School of Medicine,
Chief, Division of Endocrinology,
Harbor-UCLA Medical Center,
Torrance, California

MICHAEL TUCK, M.D.
Associate Professor of Medicine,
UCLA School of Medicine,
Chief of Endocrinology-Metabolism,
Sepulveda VA Hospital,
Sepulveda, California

RICHARD E. WEITZMAN, M.D.*
Assistant Professor of Medicine,
UCLA School of Medicine,
Director, Hypertension Services,
Harbor-UCLA Medical Center,
Torrance, California

* Deceased

Contents

CHAPTER 1

Pituitary Disease

Harold E. Carlson

HYPOPITUITARISM

Etiology

Hypofunction of the pituitary gland may result from a number of causes, which may destroy either all or part of the gland, or may interfere with the delivery of releasing (and inhibiting) factors from the hypothalamus. The causes of hypopituitarism are:

1. Neoplasms Involving Pituitary
   a. Pituitary adenoma
   b. Craniopharyngioma
   c. Metastatic or primary carcinoma (rare)
2. Granulomas
   a. Histiocytosis-X
   b. Sarcoidosis
3. Infections
   a. Tuberculosis
   b. Syphilis
   c. Fungi
   d. Pyogenic
4. Hemochromatosis
5. Aneurysm of Internal Carotid Artery
6. Infarction
   a. Post-partum necrosis (Sheehan's syndrome)
   b. Cerebrovascular disease (in diabetes mellitus)
   c. Traumatic
7. Idiopathic or Genetic
   a. Deficiency of pituitary hormones
   b. Synthesis of abnormal hormone
8. Primary Involvement of Hypothalamus
   a. Tumors (e.g., glioma, craniopharyngioma)
   b. Granulomas—sarcoidosis, histiocytosis X
   c. Trauma
   d. Idiopathic or genetic deficiency of releasing factors

e. Midline CNS structural anomalies with hypothalamic involvement

9. Iatrogenic
   a. Surgical hypophysectomy
   b. Cryohypophysectomy
   c. Stalk section
   d. Radiation

Signs and Symptoms

A variety of signs and symptoms can result from the specific hormone deficiencies produced; any combination of hormone losses may occur, although growth hormone (GH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are more commonly lost, while thyroid-stimulating hormone (TSH), prolactin (PRL), and adrenocorticotropic hormone (ACTH) are less often affected. Approximately 90% of the pituitary must be destroyed for clinical hypopituitarism to be evident.

Growth hormone deficiency produces short stature and, occasionally, fasting hypoglycemia in children; adults may develop fine facial wrinkling. Deficiency of gonadotropins (LH and FSH) leads to delayed puberty in children and hypogonadism in adults (decreased libido and potency in men, amenorrhea in women, and some loss of body hair in both sexes). Decreased ACTH secretion produces hypocortisolism with weakness and hypotension, usually normal serum potassium, loss of body hair, and poor tanning of the skin. TSH lack leads to hypothyroidism, and prolactin deficiency produces failure of lactation.

Diagnostic Tests

Hormonal deficiencies may be documented by measurement of serum hormone concentrations under appropriate circumstances. Such measurements may be useful in confirming the diagnosis of hypopituitarism and in determining the need for replacement therapy.

Growth Hormone

Under basal conditions, serum GH concentrations are normally low, and indistinguishable from those seen in hypopituitarism; therefore, provocative tests must be performed to assess GH secretory reserve capacity. Three tests are commonly used for this purpose; all are performed in a fasting state:

1. *L-dopa*—500 mg is given by mouth (250 mg in subjects weighing less than 60 kg). Serum GH is measured 60 and 90 minutes after L-dopa ingestion.

2. *Insulin hypoglycemia*—0.05 to 0.15 units/kg body weight of regular insulin is injected as an intravenous bolus. (The larger dose is given to obese patients, who are likely to be insulin-resistant, while the smaller

dose is given to patients who are likely to be overly sensitive to insulin due to suspected GH or ACTH deficiency.) Blood glucose is measured at zero, +30, and +60 minutes (the glucose nadir usually occurs at +30 minutes); serum GH is measured at +45, +60, and +90 minutes. Most patients will develop palpitations, sweating, and nervousness at the glucose nadir; a physician should be nearby to abort the test (with 50% intravenous glucose) if severe hypoglycemia develops (loss of consciousness, seizures).

3. *Arginine infusion*—30 g of arginine hydrochloride is infused intravenously over 30 minutes; serum GH is measured at +60 and +90 minutes.

About 95% of normal subjects respond to any of the preceding tests with a peak serum GH of at least 7 ng/ml; responses in men and prepubertal children are lower than those seen in women, and may be enhanced by 2 to 3 days of estrogen therapy (e.g., 5 mg diethylstilbestrol by mouth daily). Obesity and hypothyroidism both blunt GH responses to all stimuli; appropriate treatment of hypothyroidism reverses this situation.

Gonadotropins

In the presence of hypogonadism (i.e., amenorrhea and low serum estradiol in women; poor libido, impotence, and low serum testosterone in men), normal feedback relationships would lead to an increase in LH and FSH secretion by the pituitary. Thus, finding low or even normal serum LH and FSH in a hypogonadal patient implies the presence of pituitary or hypothalamic disease. Since secretion of LH and testosterone is pulsatile and episodic, it is useful to pool three 5-ml blood specimens drawn 10 to 15 minutes apart and submit the pooled sample as a single specimen; this averaging effect will lead to a more meaningful result in the basal LH and testosterone determinations. Patients with pituitary destruction will not respond to exogenous LH-RH* (100-μg intravenous bolus) by increasing their serum LH and FSH, while patients with pure hypothalamic disease and intact pituitaries will often show a rise in serum LH and FSH following LH-RH injection; 5 to 7 days of "priming" with daily LH-RH injections may be necessary to bring out this response. LH-RH is currently available only on an investigational basis.

ACTH

In theory, finding a low or normal plasma ACTH level in a hypoadrenal patient should demonstrate the presence of hypothalamic-pituitary disease. However, plasma ACTH is quite difficult to measure reliably. Thus, we usually depend on two indirect tests of ACTH secretion:

* Synthetic gonadotropin-releasing hormone.

1. *Insulin hypoglycemia*—performed as for GH testing described earlier. Serum cortisol should be measured at zero, +60, and +90 minutes; a normal response is a rise in serum cortisol of at least 7 μg/100 ml reaching peak levels of at least 20 μg/100 ml.

2. *Metyrapone*—This drug blocks the final step in cortisol biosynthesis. In the presence of an intact hypothalamic-pituitary-adrenal axis, ACTH secretion increases following metyrapone administration, leading to increased adrenal secretion of the immediate precursor of cortisol, 11-deoxycortisol (compound S). In the convenient overnight metyrapone test, 3 g of metyrapone (2 g for subjects weighing less than 60 kg) are given orally at bedtime with a snack (this drug may result in nausea without the snack). The next morning at 8 A.M. (±30 minutes), a single serum sample is obtained for cortisol and compound S determination. In a normal response, compound S levels are ≥ 8 μg/100 ml. If a subnormal rise in compound S is seen, check to be sure that serum cortisol was sufficiently lowered by the metyrapone (to < 5 μg/100 ml); if cortisol is > 5 μg/100 ml, poor absorption of the metyrapone may have occurred, and the test could be repeated at a higher dose or the insulin hypoglycemia test performed.

TSH

In the presence of hypothyroidism, a low or normal serum TSH indicates pituitary or hypothalamic disease. If serum TSH responds to TRH† (500-μg intravenous bolus) with a rise in serum TSH to a peak > 5 μU/ml, hypothalamic disease may be present (especially if the serum TSH peak is delayed (60 minutes or more after TRH injection) or prolonged (lasting 30 minutes or more).

Prolactin

Prolactin deficiency can be most easily documented by measuring serum PRL during a TRH test (described previously). Normally, serum PRL at least doubles, reaching peak levels of more than 10 to 12 ng/ml at 15 to 30 minutes after TRH injection. Since PRL is predominantly under hypothalamic inhibitory control, patients with hypothalamic disease but intact pituitaries often have an elevated basal serum PRL (> 12 ng/ml in men; > 15 ng/ml in women in our laboratory). Some of the causes of hyperprolactinemia are:

1. Prolactin-Producing Pituitary Tumors
2. Anatomic Interference with Prolactin-Inhibiting Factor Secretion
   a. Hypothalamic destruction
   b. Stalk section
3. Altered Physiologic States
   a. Pregnancy

†Synthetic thyrotropin-releasing hormone.

b. Nursing or nipple stimulation
c. Chest wall lesions
d. Pseudocyesis
e. Hypothyroidism
f. Stress (pain, anxiety, exercise, surgery)
g. Sleep
h. Hypoglycemia
i. Coitus
j. Chronic renal failure

4. Drugs
   a. Phenothiazines
   b. Butyrophenones (e.g., haloperidol)
   c. Reserpine
   d. Cimetidine (intravenous)
   e. Metoclopramide
   f. Tricyclic antidepressants
   g. Estrogens
   h. Alpha-methyldopa
   i. Arginine infusion

Anatomic Features

In addition to hormonal deficiencies, lesions producing hypopituitarism may also produce local signs and symptoms due to the presence of an intracranial mass. Patients with sellar or parasellar mass lesions may complain of headaches (usually retro-orbital or temporal), visual field defects (classically a bitemporal hemianopsia due to chiasmal compression), and diplopia related to extraocular cranial nerve palsies (especially the third). The presence and extent of such mass lesions are usually documented by the ophthalmologic and radiologic examinations listed later; such examinations often allow a specific diagnosis to be made (such as a tumor) and specific therapy to be selected (surgery versus radiation; see later). Visual field examination and ocular motility testing will document optic chiasm and cranial nerve compression. Plain skull x-rays and cone-down views may reveal generalized enlargement or destruction of the sella turcica as well as parasellar calcification suggestive of craniopharyngioma. A "double floor" of the sella (seen on lateral skull x-ray) suggests the presence of localized or asymmetrical expansion of the sellar walls, often due to a small pituitary tumor or microadenoma (Fig. 1–1); this localized expansion is often better seen on sellar polytomography with cuts at 1 to 2 mm intervals. Carotid angiography is most useful in defining the vascular anatomy prior to neurosurgical procedures and in ruling out aneurysms, a rare cause of hypopituitarism. The pneumoencephalogram remains the definitive procedure for defining suprasellar extension; as such, it is especially helpful to the neurosurgeon. Additionally, the pneumoenceph-

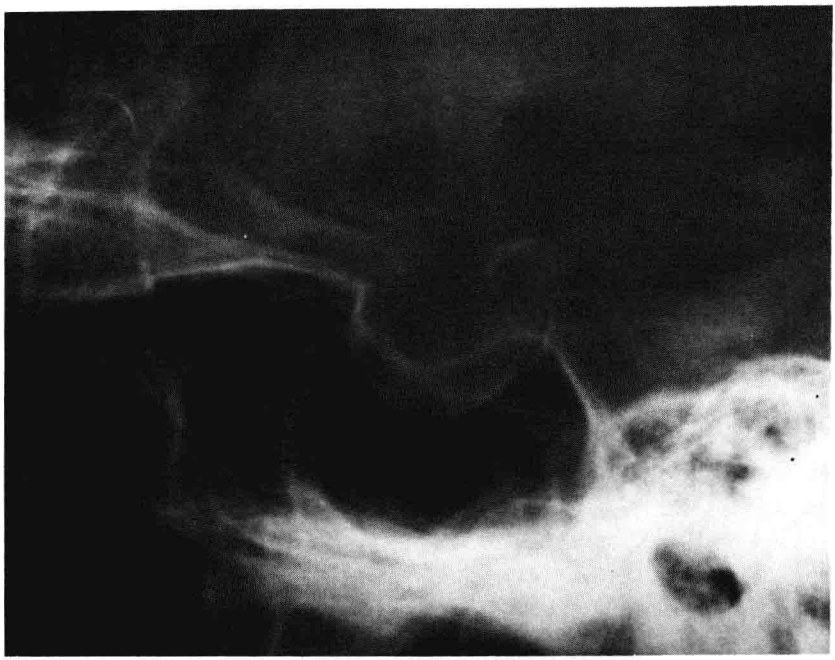

Figure 1–1. Asymmetrical expansion of the sella turcica seen as a "double floor" on a lateral skull radiograph. Polytomography would more definitively localize such an abnormality.

alogram is useful in diagnosing the "empty sella" syndrome—usually a benign condition associated with an incompetent diaphragma sellae (Fig. 1–2). A limited pneumoencephalogram, in which no attempt is made to fill the lateral ventricles or introduce large volumes of air over the cerebral hemispheres, is not as uncomfortable for the patient as the full procedure; however, lumbar pneumoencephalography may be dangerous and should be avoided in patients with evidence of raised intracranial pressure due to mass lesions. Radionuclide brain scans and computed tomography scans are most useful in evaluating fairly large suprasellar lesions, although further refinements in the techniques of computed tomography may make it more consistently useful in investigating smaller, intrasellar masses.

Therapy

The treatment of hypopituitarism is concerned with both hormonal replacement and correction of anatomic abnormalities. The need for hormone replacement should be determined by the results of specific hormone measurements, as previously described.

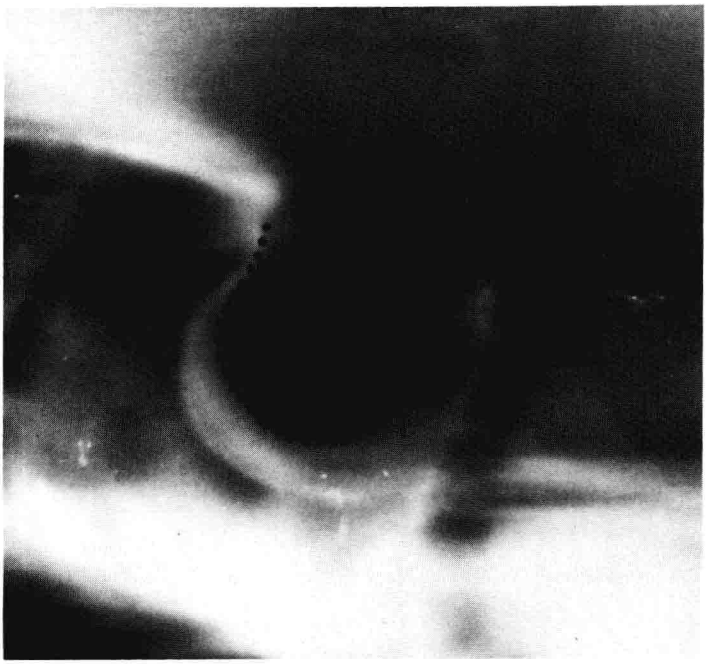

Figure 1–2. Air in the sella turcica demonstrated during a pneumoencephalogram in a patient with a primary "empty sella"; the air is outlined by the dotted line.

Hormone Replacement (Table 1–1)

Growth Hormone

GH is given by intramuscular injection in an initial dose of 2 units three times per week. Only patients with unfused epiphyses should be given GH as it will not promote linear bone growth once epiphyseal fusion has occurred. In practice, little additional growth is achieved in patients with a bone age over 14 years. Human growth hormone is available from the National Pituitary Agency on a research basis or from Hoechst commercially at a cost of about $2400 per year. Occasionally, GH therapy induces hypothyroidism in children, apparently by a suppressive effect on TSH secretion; therefore, serum thyroxine should be measured periodically in patients receiving GH therapy.

Gonadotropins

Unless fertility is desired, gonadal steroid end-products are provided; these agents promote the development or retention of the apppropriate male or female sexual characteristics. In women, a low-estrogen oral contraceptive pill is a convenient mode of therapy; in men, injectable