Endocrine Pathophysiology:

A Patient-Oriented Approach

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Second Edition

Lea & Febiger 1982 · Philadelphia

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106
U.S.A.

First Edition, 1977
Reprinted, 1978

Translations:
First Edition—
Spanish Edition by Nueva Editorial Interamericana, S.A. de C.V., Mexico, D.F., Mexico—1981

Library of Congress Cataloging in Publication Data
Main entry under title:

Endocrine pathophysiology.

Bibliography: p.
Includes index.
1. Clinical endocrinology. 2. Physiology, Pathological. I. Hershman, Jerome M. [DNLM: 1. Endocrine diseases—Physiopathology. WK100 H572e]
RC649.E52 1982 616.4'07 82-7183
ISBN 0-8121-0840-X AACR2

PRINTED IN THE UNITED STATES OF AMERICA

Print Number: 3 2 1

Preface

The purpose of this volume is to give medical students an understanding of the pathophysiology of endocrine diseases. The authors assume that the student has taken an introductory course in endocrine physiology and biochemistry, so the review of basic endocrinology in each chapter covers only those topics most relevant to clinical medicine.

Endocrine disorders mainly involve either excessive or decreased secretion of specific hormones. The text presents methods of testing specific glandular function with static measurements of hormone levels and effects, with dynamic stimulation tests for evaluation of hypofunction of the endocrine gland, and with dynamic suppression tests for diagnosis of hyperfunctional states.

Systematic discussions of endocrine pathophysiology elucidate the symptoms and signs of endocrine diseases. The chapters also present the principles of therapy for each disorder and relevant clinical pharmacology. Descriptions of endocrine pathology have been kept to a minimum.

Case studies of patients with endocrine disorders illustrate the clinical findings and diagnostic methods. Questions pertaining to these patients test the reader's understanding of the material and emphasize clinical concepts. The answers to the questions appear in a separate section at the end of the text. Students at the UCLA School of Medicine have found that this patient-oriented approach more actively involves them and aids comprehension.

In the five years since the first edition appeared, there have been significant advances in understanding endocrine disease. These advances have been incorporated into each chapter, and obsolete material has been deleted. The new chapter on calcium and phosphate and metabolic bone disease emphasizes the recent, exciting developments on the role of vitamin D in bone physiology and disease.

Although this volume is aimed primarily at medical students, residents in medicine, internists, and family physicians may find it useful as a succinct review of current concepts in clinical endocrinology.

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Contents

CHAPTER 1

Principles of Clinical Endocrinology

Jerome M. Hershman

Clinical disorders of endocrine glands are mainly of two types: hyperfunction and hypofunction. Hyperfunction denotes excessive secretion of the hormone. The clinical findings, i.e., the signs and symptoms, of the disorder reflect how oversecretion affects target tissues. Hypofunction denotes deficient secretion of the hormone; the resulting signs and symptoms occur because the amount of this hormone is insufficient to achieve its normal effect on target tissues.

The concept of hyperfunction and hypofunction of endocrine glands implies that these states differ from normal hormone secretion. Unfortunately, the range of normalcy of many hormone measurements overlaps both deficiency and excess of hormonal production and hormonal blood levels. Single baseline values rarely can be used to establish a definitive diagnosis. The physiologic concept of feedback control also serves as a basis for diagnosing hyperfunction and hypofunction of endocrine glands and allows each hormone system to be considered dynamically.

NEGATIVE FEEDBACK

Pituitary tropic hormones, e.g., thyroid-stimulating hormone (TSH) or adrenocorticotropic hormone (ACTH), stimulate the target organs (thyroid or adrenal in this case) to release the target gland hormones (thyroxine (T_4) and triiodothyronine (T_3) or cortisol). In turn, elevated levels of the target gland hormone feed back on the pituitary to inhibit secretion of the tropic hormone. The corollary is that the pituitary detects low levels of the target gland hormone and thus increases its tropic hormone secretion, which causes increased secretion of the target gland hormone. Consider the examples of TSH-T_4 and T_3 or ACTH-cortisol in terms of a need to increase the output of the target gland hormone. Application of this concept to all hormones aids understanding of clinical diagnostic tests.

An x-y plot of tropic versus target gland hormone levels in the blood (Fig. 1–1) illustrates useful dynamic concepts and aids understanding of clinical jargon. Consider the possible levels of ACTH-cortisol or TSH-T_4 and T_3 based on Figure 1–1.

Hypothalamic hormones, secreted into a portal venous system that reaches the pituitary directly, regulate secretion of the pituitary hormones. For each pituitary hormone, a hypothalamic releasing hormone (or factor) exists, and for some pituitary hormones, hypothalamic factors inhibit release of the pituitary hormone. The hypothalamic hormones are useful diagnostic tools for testing the response of the pituitary gland and the target glands. Various chapters detail the clinical application of the hypothalamic hormones and the stimuli that alter their secretion.

CATEGORIES OF ENDOCRINE FUNCTION TESTS

Measurement of the basal level of hormone in blood or urine may be satisfactory for making a diagnosis of hyperfunction or hypofunction when the disorder is severe, especially when the tests illustrate normal feedback relationships; e.g., low T_4 in serum and high TSH in serum indicate primary hypothyroidism.

Stimulation Test. Evaluation of secretory reserve by a *stimulation* test is useful for diagnosing hypofunction and for detecting impaired secretory reserve.

Suppression Test. These tests are useful for diagnosis of hyperfunction because the hyperfunctioning gland by definition is not operating under normal control mechanisms; suppression may be abnormal quantitatively or quali-

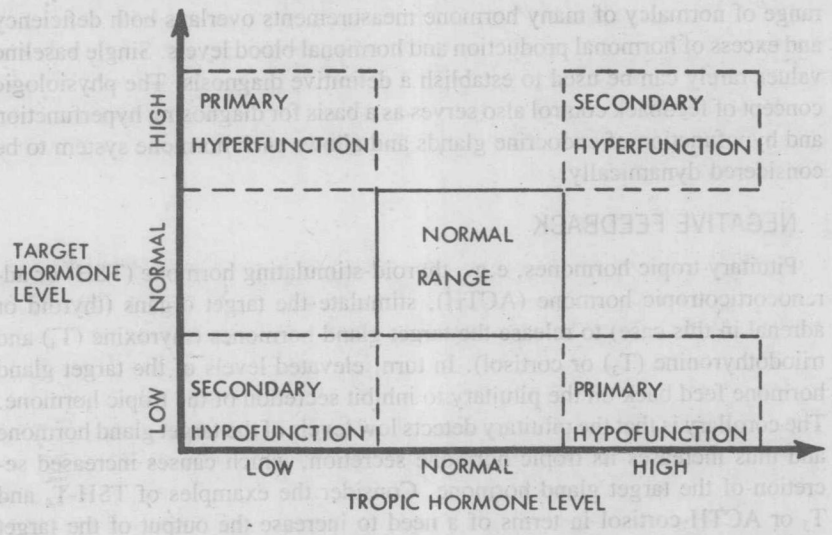

Figure 1–1. Tropic (pituitary) hormone blood level versus target hormone level to illustrate abnormal functional states.

tatively. By negative feedback control the pituitary gland may be "reset" to respond to high levels of the suppressing hormone, e.g., pituitary ACTH secretion in Cushing's disease, which is discussed later. On the other hand, the gland may be autonomous and secreting without any control, e.g., an adrenal adenoma causing hypercortisolism.

Table 1–1 shows the general scheme of interpretation of suppression and stimulation tests.

TYPES OF HORMONE MEASUREMENTS

These techniques are usually applied to blood serum (or plasma) and urine; rarely are they applied to tissue extracts.

Bioassay. It should be specific; often it is not sensitive for physiologic levels of hormones; moreover it is tedious and expensive.

Chemical Measurement. This procedure measures the hormone, e.g., plasma cortisol by fluorimetry, or it measures a physiologic consequence, e.g., blood glucose as an index of insulin secretion.

Radioimmunoassay. A specific antibody is used to recognize the hormone, but the antibody may also detect a biologically inactive portion of the molecule. Because these assays are so sensitive, they are used extensively to measure blood levels of hormones.

Radioreceptor Assays. These biologically specific tests may be highly sensitive, e.g., using thyroxine-binding globulin as a specific receptor of T_4, or plasma membranes of target organs as receptors for peptide hormones.

Table 1–1. General Scheme for Interpretation of Suppression and Stimulation Tests

Evaluation of hyperfunction		
Baseline hormone level or secretion rate	*Suppression test*	*Interpretation of function*
Normal	Normal	Normal
Elevated	Normal	Normal
Elevated	Nonsuppressible	*Hyperfunction
Evaluation of hypofunction		
Baseline hormone level or secretion rate	*Stimulation test*	*Interpretation of function*
Normal	Normal	Normal
Low	Normal	Normal
Low	Nonstimulable	Hypofunction
"Low normal"	Nonstimulable	†Impaired reserve function

*Degree of hyperfunction varies from mild to severe.

†Patient may be asymptomatic or have symptoms and signs of hypofunction.

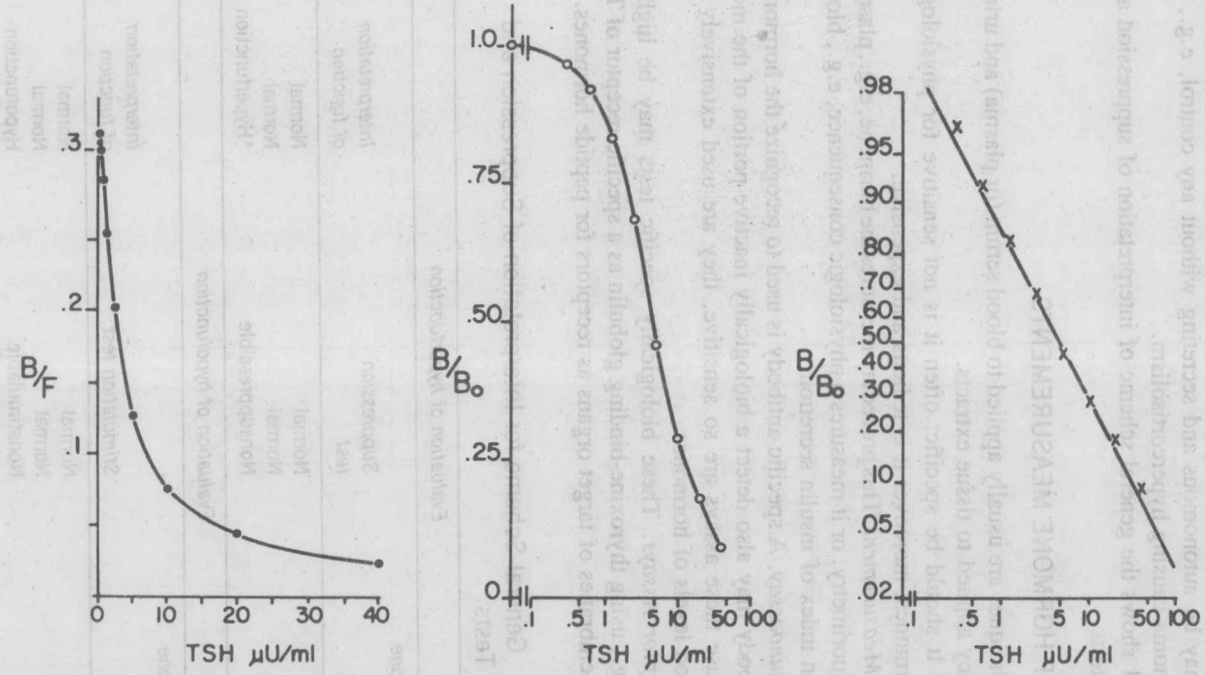

Figure 1–2. Standard curves for the radioimmunoassay of TSH plotted in three different ways: (left) bound/free labeled TSH versus TSH concentration; (middle) bound/bound at 0 dose (B/Bo) versus TSH concentration, log scale; (right) B/Bo on a logit scale (logit $y = \ln\frac{y}{1-y}$) versus TSH concentration, log scale.

Metabolic Effects. This test checks the hormone's effect on a target tissue, e.g., speed of reflex contraction to assess the effect of thyroid hormone.

Clinical Assessment Only. In some cases, there is no readily available bioassay, or the clinical situation may provide all of the bioassay data needed; e.g., normal menstrual cycles indicate integrity of the hypothalamic-pituitary-gonadal axis in women.

The inside cover contains a table of normal hormone concentrations. These values differ slightly among laboratories, depending on the details of methodology. Minor departures from the values in the table are found in some chapters. For the student, pathophysiologic concepts are more important than sharply defined (but often arbitrary) limits of normal.

TERMS

The following terms are used commonly in clinical endocrinology.

Primary Hyperfunction. Hypersection of a hormone usually due to tumor or disease of an endocrine gland itself.

Secondary Hyperfunction. Hypersecretion of a hormone produced by excessive stimulation from its tropic hormone or its physiologic stimulators; no disease of the gland per se.

Primary Hypofunction. Hyposecretion of a hormone due to disease of the gland of secretion.

Secondary Hypofunction. Hyposecretion of a hormone due to lack of a tropic hormone or lack of the physiologic stimulators.

Suppression Test. Administration of the suppressor to test autonomy of hormonal secretion.

Stimulation Test. Administration of the specific stimulator to test hormonal secretory reserve of the gland.

Secretion Rate. Amount of hormone secreted per unit of time.

Production Rate. Amount of hormone produced outside the gland plus that amount secreted by the gland per unit of time.

Half-Life in Blood. Time for blood level of hormone to fall to half of its original value.

Protein-Bound Fraction of Hormone. That percentage of hormone bound to its specific plasma binding protein and therefore considered to be physiologically inactive.

Free or Unbound Fraction. That percentage of the plasma hormone not protein bound—the physiologically active fraction, presumably.

RADIOIMMUNOASSAY

In the radioimmunoassay of hormones, the following reaction occurs:

$$H + Ab \rightleftharpoons H\text{-}Ab$$

$$*H + Ab \rightleftharpoons *H\text{-}Ab$$

where H is the unlabeled hormone (antigen), *H is the radioactive hormone tracer, Ab is the antibody to the hormone, and H-Ab (or *H-Ab) is the hormone-antibody complex. *H and Ab are added to the reaction tube in fixed amounts. H represents the hormone in the standards or unknown serum. The antibody has the same affinity for *H as for H. At equilibrium, the amount of *H bound to Ab (*H-Ab) varies inversely with the amount of hormone (H) added to the tube. With large amounts of H, *H represents a small proportion of total hormone (H + *H), and the antibody binds only a small proportion of the tracer hormone. The *H-Ab complex is separated from the free (unbound) *H and measured in a radioactivity counter.

The data for the standard curve are plotted as shown in Figure 1–2, a radioimmunoassay of TSH. In this assay, varying concentrations of TSH are added to make up the standard curve, and TSH labeled with ^{125}I is the tracer. The TSH bound to the antibody is separated from the free TSH, and the bound labeled TSH (*H-Ab) is counted. The result is often expressed as a ratio of bound counts, B, for a given sample to counts bound at 0 hormone concentration, Bo. Unknowns can be read from each of the standard curves in the different plots. For example, in Figure 1–2, an unknown serum containing a concentration of 5 μU/ml would give a B/F (Bound/Free = *H-Ab/*H) of 0.126 equivalent to 5 μU/ml (left panel). In the plot of B/Bo versus log TSH (middle panel), the B/Bo of 0.45 also indicates a serum TSH of 5 μU/ml. The straight line representation of the plot of the logit of B/Bo versus log TSH (right panel) has computational advantages because it gives a straight line for the standard curve.

The principal advantage of radioimmunoassay is its great sensitivity, which depends on the high affinity of the antibody for the hormone. These systems can detect hormone concentrations in serum of 10^{-7} M to 10^{-12} M in various assays. Although the assays are generally specific for the given hormone, they may also measure hormone metabolites or precursors devoid of biologic activity. In fact, the recognition sites of the antibody may be directed against a biologically inactive portion of the hormone molecule. This disadvantage may be overcome by replacing the antibody with a naturally occurring biologic receptor for the hormone. Radioreceptor assays presently under development are the next generation of hormone assays.

CHAPTER 2

Pituitary Disease

Harold E. Carlson

EVALUATION OF ANTERIOR PITUITARY FUNCTION

As described in Chapter 1, the function of an endocrine gland is usually assessed by means of specific stimulation and suppression tests, which make use of known normal responses to perturbation in homeostatic regulatory mechanisms. For the pituitary gland, such tests are commonly used to evaluate the secretory status of most of the individual hormones. The following sections briefly cover the structures and functions of the pituitary hormones, along with the factors (both physiologic and pharmacologic) that alter and regulate their secretion. Table 2–1 summarizes clinically useful pituitary stimulation and suppression tests.

Human Adrenocorticotropic Hormone (ACTH)

ACTH is a single-chain polypeptide of 39 amino acids whose principal function is the stimulation of cortisol production by the adrenal cortex. Like most polypeptide hormones, ACTH appears to act by binding to a specific cell membrane receptor and activating adenylate cyclase, which raises intra-

Table 2–1. Clinically Useful Tests of Pituitary Function

Hormone	*Stimulation test*	*Suppression tests*
ACTH	Insulin hypoglycemia Metyrapone	Dexamethasone administration
TSH	TRH	T_3 or T_4 administration (not standardized)
LH/FSH	LRH (LH-RH) Clomiphene	Testosterone or estrogen administration (not standardized)
GH	Insulin hypoglycemia Arginine infusion L-dopa	Glucose tolerance
PRL	TRH Chlorpromazine	None