Blue Book of Endocrinology

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1985
W. B. SAUNDERS COMPANY
Philadelphia London Toronto
Mexico City Rio de Janeiro Sydney Tokyo

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

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Artarmon, N.S.W. 2064, Australia

Ichibancho, Central Bldg., 22-1 Ichibancho
Chiyoda-Ku, Tokyo 102, Japan

Library of Congress Cataloging in Publication Data

Metz, R. (Robert J. S.)

Blue book of endocrinology.

1. Endocrine glands—Diseases. 2. Clinical endocrinology. I. Larson, Eric B. II. Title. [DNLM: 1. Endocrine diseases. WK 100 B658]

RC648.M47 1985 616.4 84–1361

ISBN 0–7216–5638–2

Blue Book of Endocrinology ISBN 0–7216–5638–2

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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PREFACE

An endocrinologist and an internist collaborated to produce this patient-oriented, practical teaching manual. The intent of pooling our complementary skills and perspectives was to insure a text that is sound, up to date, and stripped of material superfluous to the needs of its intended readership. The editors have designed the book to be useful for residents in medicine and family practice as well as for practicing internists and family practitioners. We hope that even physicians with advanced training in endocrinology will find this a useful review of the essentials of clinical endocrinology.

The critical physiologic, diagnostic, and therapeutic aspects of the clinically important hormonal disorders are presented in what we trust is a lucid, uncluttered, and convincing manner. Each chapter typically contains an algorithm graphically demonstrating the recommended diagnostic approach to the specific endocrinologic problems under discussion.

Other features include a section on endocrinologic emergencies, intended as a self-contained work manual to be used at the bedside. Chapters on withdrawal of glucocorticoid therapy, disorders of plasma lipids, and metabolic bone disease are included because they are commonly encountered clinical problems and because the subspecialty no man's land that they inhabit is closer to endocrinology than to the other subdivisions of internal medicine. Two special chapters are intended to enhance the practical how-to-go-about-it message of the text: one on radionuclide applications to endocrinology and one on specific neuroradiologic techniques used in the diagnosis of disorders in and around the pituitary gland.

ROBERT METZ
ERIC B. LARSON

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I

ACQUISITION OF CLINICAL SKILLS IN ENDOCRINOLOGY

Robert Metz
Eric B. Larson

The acquisition of clinical skills in endocrinology is facilitated by familiarity with certain principles and empiric rules. This introduction attempts to identify these signposts on the road to competence in clinical endocrinology.

GENERAL CONSIDERATIONS

Endocrinopathies may be so subtle in their presentation as to tax the diagnostic acumen of the most competent clinician. Quite often, however, the clinical picture is so distinctive as to be instantly recognizable. To miss an endocrinologic diagnosis is often mortifying to the physician, because like the hidden objects in children's picture puzzles, the overlooked diagnosis becomes only too obvious once it is identified by someone else. A more important reason for not overlooking or misdiagnosing clinical disorders of endocrine function is that most are readily treatable. Laboratory and imaging services can almost always provide confirmation of clinical diagnoses.

Endocrinologic disorders have, until recently, been perceived as invariably resulting from either an excess or a deficiency of circulating hormone. This classic concept remains valid for most endocrinologic disorders, but other mechanisms are now recognized. Impaired cellular response to the hormonal signal (as a result of receptor or post-receptor defects), inactivation of circulating hormones or antibody binding, and synthesis of a biologically inactive variant of the hormone may all result in a hormonal deficiency state despite an abundance of circulating hormone. Inadequate receptor function can occur when concentration of receptors is deficient, when receptors have functional or structural defects, or when receptors are already occupied by a blocking substance or are inactivated by an antibody to the receptors. Antibodies to a hormone receptor may result in either deficient or excessive hormone action. Blocking attachment of the hormone to the receptor inhibits hormone action. Conversely, antibodies to a receptor may mimic the hormonal effect, creating an apparent hormone excess state. Examples of this mechanism are hypoglycemia in certain cases of insulin receptor antibodies and hyperthyroidism in the case of antibodies to the thyroid-stimulating hormone (TSH) receptor in the thyroid gland (Graves' disease).

There are two general classes of hormones: peptides and catecholamines in one, and steroids and thyronines in the other. Their main distinguishing features are summarized in Table 1.

THE PRINCIPLE OF HORMONAL HOMEOSTASIS

Endocrine organs produce their hormones according to the dictates of feedback regulatory systems exquisitely tuned to set

Table 1. CHARACTERISTICS AND CLASSIFICATIONS OF HORMONES

FEATURE	PEPTIDES AND CATECHOLAMINES	STEROIDS AND THYRONINES
Circulation	Free	Bound to serum proteins
Plasma concentrations	Fluctuate rapidly	Slow variations
Receptors	Cell surface	Intracellular
Primary mechanism	Activate preformed enzymes	Stimulate *de novo* protein synthesis
Onset of action	Rapid (seconds to minutes)	Slow (hours)

points that vary according to circadian and other rhythms. The simplest systems are those in which the synthesis and secretion of a hormone is regulated by the plasma concentration of the metabolite or metabolites that the hormone regulates. Examples of this relationship include that of parathyroid hormone with ionized calcium and that of insulin with glucose. Other factors may modify the feedback relationship. For example, insulin secretion is affected not only by plasma glucose concentration but also by neurologic stimuli, several gastrointestinal hormones, and specific amino acids.

In some homeostatic systems the hormone functions as only one limb of the feedback loop, and additional mechanisms are necessary for physiologic regulation of that particular system. For instance, vasopressin, the antidiuretic hormone, cannot by itself maintain body water homeostasis, which requires in addition the nonhormonal mechanism of conscious recognition of and response to thirst.

The most complex control mechanisms currently recognized involve cascades of hormones set in motion by neurologic or neuroendocrine mechanisms. Figure 1 depicts in diagrammatic form an example of such a system, the regulation of ovarian function involving participation of higher brain centers, hypothalamus, pituitary, and ovary. Many of the chemical mediators have been identified, but much remains to be learned about this and similar systems involving brain–hypothalamus–pituitary–target organ interactions. Fundamental questions are still without answers. For instance, what sort of biological input stirs the brain to activate the hypothalamus to set in motion the hormonal events of puberty?

A malfunction of any component of the regulatory system will be manifested as a disorder of the last hormone in this chain. For example, when one is dealing with delayed onset of puberty, several questions arise: Has the central nervous system failed to signal the hypothalamus that the time has come for puberty? Has the hypothalamus failed to produce gonadotropin-releasing hormone? Has the pituitary failed to produce gonadotropins? Has the

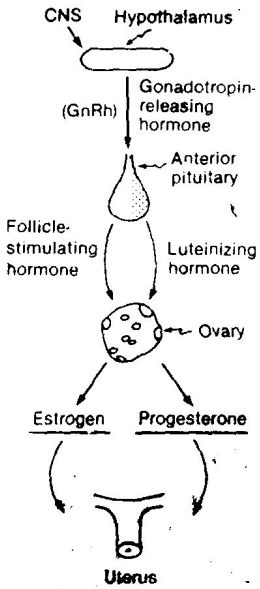

Figure 1. Regulation of ovarian function. (Adapted from Williams RH, ed: Textbook of Endocrinology. 6th ed. Philadelphia, WB Saunders, 1981.)

ovary/testis failed to produce estrogen/testosterone? Have the target organs failed to respond to the effects of the hormones? A failure at any level results in a failure of puberty, with one clinical picture (delayed puberty), a host of etiologic possibilities, and five different levels to evaluate.

Thus, in *hormone deficiency syndromes* it is necessary to identify the locus of the defect. In order for a hormone to act on its target tissue it must be (1) synthesized without a significant structural defect and in adequate quantity, (2) released appropriately, (3) further modified in the circulation or peripheral tissues in the case of certain hormones, (4) transported to the target tissue, and (5) bound to specific receptors either on the cell surface or within the cell, depending on the hormone. Even if all these functions are intact, for hormone action to occur there must also be a set of reactions triggered by the attachment of the hormone to its cellular receptor. A malfunction of any of these processes will result in a hormone deficiency state.

Hormone-resistant states were first recognized by Albright when he demonstrated parathyroid hyperplasia in patients with what he termed pseudohypoparathyroidism. This syndrome can be caused by defects at the cell membrane level of target tissues (receptor deficiencies), by cytoplasmic defects (intracellular transport defect), by a malfunction at the nuclear level (failure to synthesize N protein), or by an inability of renal tubular cells to convert 25-

hydroxy cholecalciferol (25(OH)D) to 1,25-dihydroxy cholecalciferol ($1,25(OH)_2D$). Any of these defects will produce the same metabolic effect: hypocalcemia in the presence of abundant plasma concentrations of parathyroid hormone.

Similar reasoning underlies the approach to other endocrine syndromes. *The hormone overproduction syndromes* indicate an escape of feedback regulation at any one of several levels. The most easily comprehended of the overproduction syndromes are autonomously functioning tumors, as encountered most often in the parathyroid, thyroid, islets of Langerhans, adrenal cortex, adrenal medulla, and pituitary. In most endocrine glands, tumors are the usual mechanism of hormone overproduction, the thyroid gland being the prominent exception to this rule. The most common etiology of hyperthyroidism is Graves' disease, the mechanism of which is stimulation of the TSH receptor by autoantibodies.

The possibility of exogenous hormones (factitious or iatrogenic) must be considered when evaluating apparent overproduction syndromes, especially in paramedical and medical personnel, who seem especially prone to these factitious "endocrinopathies." Surreptitious self-administration of thyroid preparations, oral antidiabetic medicines, and even insulin is occasionally encountered in clinical practice.

THE PATIENT AS A "BIOASSAY"

The patient who manifests the signs and symptoms of an endocrinopathy is, in effect, a bioassay system. To think in these terms often clarifies the diagnosis. For instance, in a woman presenting with weakness, lack of energy, and weight loss, the differential diagnosis is quite extensive because her complaints lack specificity. However, if the physician observes that she has lost her axillary hair, a specific sign of androgen deficiency enters the diagnostic equation. The adrenal cortex is a major site of androgen production in the female, so suspicion focuses on the possibility of adrenocortical insufficiency. If the patient is noted to be hyperpigmented, the presumptive diagnosis of primary adrenocortical failure is greatly strengthened, because hyperpigmentation is a "bioassay" of ACTH excess. If, in addition, the laboratory tests reveal hyperkalemia, yet another "bioassay" (aldosterone deficiency) enters the picture, and the diagnosis becomes virtually certain even before a single specific laboratory test is ordered.

At this point both the nonspecific and the specific features of adrenocortical insufficiency (glucocorticoid, androgen, and mineralocorticoid deficiency) fall into place. If, on the other hand, axillary hair is abundant, adrenocortical insufficiency is very unlikely to be the explanation for the woman's nonspecific symptoms. The "patient as a bioassay" reveals most when specific manifesta-

tions can be identified among the distracting plethora of nonspecific signs and symptoms.

If, instead of having hyperpigmentation, the patient appears pale and pallid, the clinical suspicion will focus on the possibility of pituitary failure leading to secondary androgen deficiency. Thus, skin pigmentation may be a specific bioassay for ACTH, just as axillary hair may be a specific bioassay for (adrenal) androgen in the female.

Specific telltale signs and symptoms of endocrinologic dysfunction are not invariably apparent, however. In hyperparathyroidism, for instance, it usually takes many years for the specific effects of excessive parathyroid hormone on bone and urinary tract to become apparent. The patient may present with only the nonspecific symptoms of hypercalcemia or, more commonly, with no symptoms at all, which is why in most cases the diagnosis of hyperparathyroidism is first suggested by the incidental detection of hypercalcemia on a screening "battery" of tests.

Viewing the patient as hormonal bioassay is frequently helpful in the diagnostic assessment of a variety of nonhormonal disorders that are commonly believed by the public to be of hormonal origin. Among these conditions, which probably occur more commonly than true endocrinologic disorders, are obesity, episodic diaphoresis, shedding of scalp hair in women, dysphoria, "premenstrual tension," behavioral problems in young individuals, and symptoms supposedly induced by sugar ingestion ("functional hypoglycemia"). "Hormone imbalance," a concept of very dubious scientific validity, is a diagnosis often proposed by the sufferers, who usually insist on a thorough evaluation of their various endocrinologic functions. Many such patients have already had extensive laboratory testing. Therein lies one of the potential traps in dealing with these problems: If enough laboratory tests are done, it is quite likely that one or more of the results will fall on or about the upper or lower limits of the normal range, thereby reinforcing the patient's and perhaps the physician's suspicions of a subtle endocrinologic disorder. To go along with this viewpoint will almost always involve the physician and patient in an ultimately frustrating and futile interaction. Consultant endocrinologists quite often see patients who have taken unnecessary "replacement" therapy for years despite persistence of the original symptoms. A generally reliable guide in these matters is that if the symptoms are severe, they are not likely to be caused by "borderline" abnormalities of plasma hormone concentrations.

The correct approach with regard to endocrinologic disease is to look for specific hormonal effects in these individuals. Very marked excesses of androgen may produce scalp hair loss in women but will invariably produce concomitant evidence of virilization elsewhere. The perfectly feminine-appearing woman with scalp hair loss should not undergo a work-up for androgen excess. Similarly,

if hypothyroidism is the cause of the shedding of scalp hair, the patient will almost certainly exhibit other evidence of myxedematous changes.

Obesity is rarely attributable to hormonal dysfunction. According to a reliable rule of thumb, if the obesity is massive (75 per cent or more in excess of ideal body weight) or of long standing, the cause is not hormonal. Certainly, massively obese individuals may develop a hormonal disorder, but the disorder is not the cause of the obesity. If Cushing's syndrome is suspected in an obese individual, look for the *catabolic* signs of glucocorticoid excess: muscle wasting as manifested by flat buttocks, thin thighs and flaccid abdominal musculature, fragile skin, striae, and ecchymosis. Most markedly obese individuals have large buttocks and thighs and robust skin. Hypothyroidism, the other endocrinologic disorder often considered as a cause of obesity, rarely induces more than a very moderate weight gain because the appetite usually declines in proportion to the decrease in metabolic rate. Specific signs of hypothyroidism will usually be discernible in those few patients in whom mild weight gain is in fact a result of hypothyroidism.

Impotence is another condition frequently supposed to be a manifestation of hormonal deficiency; however, psychogenic, neurologic, vascular, and pharmacologic causes far outnumber the cases of androgen deficiency. When androgen deficiency is the cause, other evidence will often be apparent.

"Functional hypoglycemia," perhaps the most common and most troublesome of the non-endocrinopathies, is discussed in Part II, Chapter 13.

In all cases of doubt, be sure to obtain *solid* laboratory confirmation. Do not be misled by "borderline" results. Other diagnoses must be sought to explain the patient's symptoms if the "bioassay" findings are inconclusive and the appropriate laboratory tests are not clearly abnormal.

There are conditions, however, in which the "bioassay" clearly indicates abnormality but in which plasma concentrations of hormones do not provide an adequate reflection of functional status. Females with hirsutism may have normal (albeit usually high-normal) levels of plasma testosterone and/or dihydroepiandrosterone. Female infertility may occur because of subtle abnormalities in gonadotropin secretion patterns. Hyperparathyroidism may be the cause of kidney stones despite plasma parathyroid hormone (and even calcium) levels within the normal range. Cases of hypothyroidism occasionally occur in which plasma thyroxine concentrations are within the normal range. These and other examples of difficulties in diagnosis are discussed in the body of the book. It may, however, be helpful in building skills as an endocrinologist to consider some of the principles of laboratory testing strategies before focusing on the specifics of individual endocrinopathies.