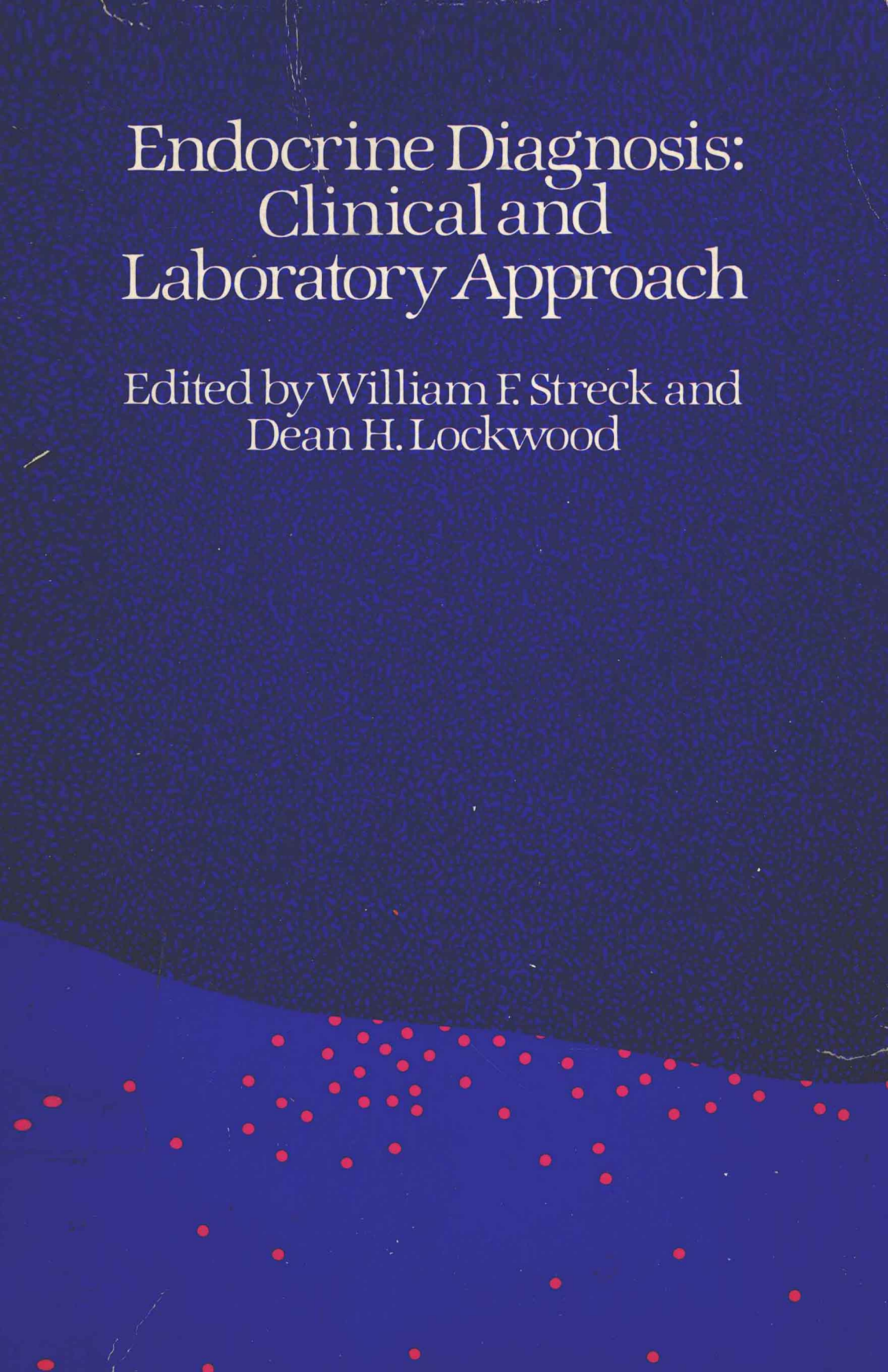
Endocrine Diagnosis: Clinical and Laboratory Approach

Edited by William F. Streck and Dean H. Lockwood



Endocrine Diagnosis

Clinical and Laboratory Approach

EDITED BY

William F. Streck, M.D.

Attending Physician, Department of Medicine, Endocrine Section, Mary Imogene Bassett Hospital, Cooperstown, New York; Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, New York, New York

Dean H. Lockwood, M.D.

Professor of Medicine and Head, Endocrine-Metabolism Unit, University of Rochester School of Medicine; Department of Medicine, Strong Memorial Hospital, Rochester, New York

LITTLE, BROWN AND COMPANY
Boston/Toronto

First Edition

Library of Congress Catalog Card No. 83- 80069
ISBN 0-316-81960-3
Printed in the United States of America
SEM

Contributing Authors

John M. Amatruda, M.D.
Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry; Endocrine-Metabolism Unit, Strong Memorial Hospital, Rochester, New York

Robert G. Brodows, M.D.
Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry; Head, Endocrine-Metabolism Division, The Genesee Hospital, Rochester, New York

S. Zane Burday, M.D.
Clinical Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry; Associate Physician, Department of Medicine, Strong Memorial Hospital, Rochester, New York

Robert G. Campbell, M.D.
Professor of Medicine and Biochemistry, University of Rochester School of Medicine and Dentistry; Director, Endocrine-Metabolism Unit, Monroe Community Hospital, Rochester, New York

William T. Cave, Jr., M.D.
Assistant Professor of Medicine, University of Rochester School of Medicine and Dentistry; Head, Endocrine Unit, St. Mary's Hospital, Rochester, New York

Zachary R. Freedman, M.D.
Assistant Professor of Medicine, University of Rochester School of Medicine and Dentistry; Endocrine-Metabolism Unit, Strong Memorial Hospital, Rochester, New York

Robert E. Heinig, M.D.
Assistant Professor of Medicine, University of Rochester School of Medicine and Dentistry; Head, Endocrine-Metabolism Unit, Rochester General Hospital, Rochester, New York

Laurence S. Jacobs, M.D.
Professor of Medicine and Director, Clinical Research Center, University of Rochester School of Medicine and Dentistry; Endocrine-Metabolism Unit, Strong Memorial Hospital, Rochester, New York

Angelo A. Licata, M.D.
Assistant Professor of Medicine, Department of Endocrinology, The Cleveland Clinic Foundation, Cleveland, Ohio

Dean H. Lockwood, M.D.
Professor of Medicine and Head, Endocrine-Metabolism Unit, University of Rochester School of Medicine and Dentistry; Department of Medicine, Strong Memorial Hospital, Rochester, New York

Lewis B. Morrow, M.D.
Professor of Medicine, Medical College of Ohio; Endocrine-Metabolism Unit, Medical College of Ohio Hospital, Toledo, Ohio

William F. Streck, M.D.
Attending Physician, Department of Medicine, Endocrine Section, Mary Imogene Bassett Hospital, Cooperstown, New York; Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, New York, New York

T. Franklin Williams, M.D.
Professor of Medicine, University of Rochester School of Medicine and Dentistry; Medical Director, Monroe Community Hospital, Rochester, New York

Paul D. Woolf, M.D.
Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry; Endocrine-Metabolism Unit, Strong Memorial Hospital, Rochester, New York

Preface

Clinical problems in medicine that are of an endocrine or metabolic nature provide unique opportunities for the integration of clinical observation and sophisticated laboratory technology. The complex array of laboratory tests available for the assessment of endocrine problems makes effective use of these tests a challenge. The expense of many of these tests makes cost-effectiveness mandatory. It is not surprising, therefore, that quite a number of books attempting to assess endocrine and metabolic problems have been published within the last several years.

This book emphasizes the *process* of diagnosis, that is, the orderly and systematic use of information to provide correct and economic solutions to endocrine diagnostic problems. This approach is somewhat different from that presented in other texts and distinguishes this book from most others. For instance, standard texts might describe the woman with polycystic ovarian disease as having elevated free testosterone levels, an LH:FSH ratio of 2:1 or greater, and an estrogen suppression test that shows decreased testosterone and/or androstenedione. This description lists the characteristics that define the polycystic ovarian syndrome, without providing a method by which they may be correctly sought or observed. However, the hirsute woman presenting for evaluation has a series of potential problems that require investigation. Therefore, this book stresses the use of methods and the sequence of investigation that will allow diagnosis of this disorder without a series of extraneous tests. Each chapter emphasizes the process by which conclusions are drawn in the assessment of endocrine disorders, and illustrates this process by means of flowcharts of Diagnostic Protocols, which are provided for each disorder. (For a list of the Diagnostic Protocols, see p. xi.)

Chapters are arranged in a standardized format, based on the premise that the physician begins with a specific clinical problem, such as hirsutism, hyperlipidemia, or hypercalcemia. From this starting point each chapter follows a format designed to complement the clinical method, in which the systematic gathering of information, selection of tests, delineation of decision points, and review of data are used to reach a diagnostic conclusion.

In the first part of each chapter, Clinical Considerations, the clinical characteristics of various disorders that enter the differential diagnosis for a given problem are discussed. Emphasis on laboratory characteristics is kept to a minimum in this section.

The second section, Diagnostic Methods, lists in sequence the major tests available for the assessment of the endocrine and metabolic disorder under discussion. Each test is discussed briefly. Limitations of the tests are touched on and normal values are provided.

The third section of each chapter, Diagnostic Protocol, incorporates some of the clinical clues and provides a systematic way to order labora-

tory tests and make decisions in the investigation of a given problem. It should be emphasized that these are simply proposed means to approach problems, since there are certainly few absolute ways to deal with any given problem. The suggestions in this section represent in large part the clinical approach used in the Endocrine-Metabolism Unit of the University of Rochester School of Medicine and Dentistry. We believe they are fairly comprehensive.

The fourth section of each chapter, Discussion, recognizes the variabilities in approach and the fact that there are limitations to any test in whatever sequence it has been obtained. Thus, this section reviews the limitations of the testing protocol, the pros and cons of various tests, and the rationale for the tests as provided.

Current references are provided throughout each chapter to allow the reader to seek more definitive information on the recommendations, clinical pictures, or procedures described in this book. We have included these references to provide the reader with the opportunity to enhance the practical application of knowledge that each chapter attempts to provide.

W. F. S.
D. H. L.

Endocrine Diagnosis

Clinical and Laboratory Approach

NOTICE

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contents

List of Diagnostic Protocols

Diagnostic Protocols are provided for disorders described in this book for two reasons. The first is very practical. When a clinical problem is encountered, there is often uncertainty as to the most efficient way to *initiate an evaluation*. The problem-focused protocols are designed to allow a correct, efficient, and readily accessible first step in the approach to endocrine diagnostic problems. Simply by referring to these protocols, appropriate tests may be reviewed and inappropriate or less useful tests avoided.

The initiation of an evaluation unlocks a cascade of clinical and laboratory alternatives; at each level, decisions must be made until a diagnosis emerges. Thus, the second use of the Diagnostic Protocols is to provide the framework to *complete an evaluation* of a given problem. The approaches recommended are reviewed and discussed in the corresponding text for each chapter.

1 Diabetes Mellitus

Dean H. Lockwood

Diabetes mellitus is a complex metabolic disorder in which the basic defect appears to be a relative or absolute lack of insulin. Although not clearly defined, viral, immunologic, and genetic factors have been implicated as playing causal roles [2,13,17]. Because of the increased longevity and reproductive capabilities of diabetics in the past 60 years, the prevalence of this disease is continually increasing. Conservative estimates suggest that approximately 5% of the population of the United States is afflicted with this disorder. Currently, diabetes ranks fifth as a cause of death in the United States and is the major cause of blindness and loss of limb in the adult population. The economic impact of diabetes and its complications was estimated to be about 8 billion dollars per year in 1979. These grim statistics should serve to emphasize the importance of making a correct diagnosis as early as possible, with the hope that proper management will minimize morbidity and delay mortality. As will be discussed subsequently, the criteria for the diagnosis of diabetes have been revised substantially.

CLINICAL CONSIDERATIONS

Physicians have long recognized that there are two general types of diabetes which can usually be distinguished by their clinical presentation. These two categories, which were formerly termed *juvenile-onset* and *maturity-onset diabetes*, have been recently reclassified as type I, *ketosis-prone*, or *insulin-dependent diabetes*, and type II, *nonketosis-prone*, *non-insulin-dependent diabetes.*

Type I Diabetes

In patients with type I diabetes, the presenting symptoms are often dramatic because there is an associated severe insulin deficiency. These patients, who are usually less than 20 years of age, may have the rapid development of polyuria, polydipsia, and polyphagia, with associated weight loss. Lack of insulin in this situation ultimately leads to severe dehydration, ketoacidosis, and eventually coma. Studies of the etiology of type I diabetes suggest the involvement of both genetic and environmental factors [13]. Insulin-dependent diabetes is frequently associated with certain histocompatibility antigen (HLA) types and abnormal immune responses, including islet cell antibodies. Furthermore, there is mounting evidence to suggest that certain cases are the result of viral infections.

Type II Diabetes

An insidious onset usually characterizes type II diabetes mellitus, which is frequently seen in older obese patients. In fact, the diagnosis is fre-

quently made on the basis of laboratory information obtained when the patient is without symptoms, as during a routine examination. However, some patients will develop signs and symptoms of significant insulin deficiency, especially under conditions in which pancreatic insulin output is stressed. This may occur with pregnancy, obesity, and infection and in association with certain drug therapies. The patient may complain of blurring of vision and myopia, as well as episodes of recurrent infection, such as carbuncles, furuncles, urinary tract infections, monilial vaginitis in the female, and balanitis in the male. Although these patients are considered to be partially insulin-deficient, it is becoming increasingly apparent that most type II diabetics also have insulin resistance at the level of the target tissue. In addition, some patients can present with transient postprandial hypoglycemia, and others, at the time of diagnosis, may have evidence of the chronic complications of the disease. Patients with type II diabetes may require insulin for correction of hyperglycemia, but they are not considered insulin-dependent or ketosis-prone. Genetic susceptibility is felt to be a strong etiologic factor, but unlike type I diabetes, there is no association with the HLAs.

Impaired Glucose Tolerance

Until recently, the proposed criteria for the diagnosis of diabetes based on fasting plasma glucose levels and plasma glucose levels obtained during an oral glucose tolerance test have varied widely. The differing criteria, coupled with population studies that frequently have been unable to distinguish between the upper limits of normal and mild diabetes, have led to considerable confusion concerning the appropriate diagnosis. More recently, epidemiologic studies have strongly suggested that our criteria for diagnosis have been inappropriate, and in general, physicians have overdiagnosed the disease. Epidemiologic studies of diabetes in the Pima Indians [1] have revealed a bimodal distribution for both fasting plasma glucose and the two-hour level obtained during an oral glucose tolerance test. This study convincingly demonstrates that diabetes definitely persists and is associated with the well-known complications when fasting plasma glucose is above 140 mg/dl and the two-hour sample is above 200 to 240 mg/dl. Other studies, carried out in Great Britain and the United States, support these criteria [6, 15]. Of greater interest is the observation that patients with milder degrees of glucose intolerance over time can decompensate to frank diabetes, revert to normal glucose tolerance, or remain "chemical diabetics." Because decompensation occurs at a rate of only 1 to 5% per year, a new classification termed *impaired glucose tolerance* has been established for this group.

In addition to the signs and symptoms already discussed, there are three other clinical situations that have an increased association with diabetes and may prompt the physician to pursue the diagnosis of diabetes vigorously.

Table 1-1. Commonly Used Drugs Affecting Glucose Tolerance

Hyperglycemia	*Hypoglycemia*
Amitriptyline	Biguanides
Caffeine	Ethanol
Catecholamines	Sulfonamides
Chlorthalidone	Sulfonylureas
Clonidine	
Corticosteroids	
Diphenylhydantoin	
Furosemide	
Haloperidol	
Imipramine	
Indomethacin	
Lithium carbonate	
Oral contraceptives	
Phenothiazines	
Thiazides	

Pregnancy

Several studies indicate that good control of diabetic metabolic abnormalities during the third trimester of pregnancy reduces neonatal morbidity and mortality [8]. More recently, additional evidence strongly suggests that good control beginning at conception may prevent congenital malformations [10]. Thus, diabetes mellitus should be strongly considered in pregnant women who have any of the following conditions: (1) glucosuria; (2) a family history of diabetes in a first-degree relative; (3) a history of spontaneous abortion, stillbirth, or fetal malformations in previous pregnancies; (4) previous delivery of an offspring weighing more than 9 pounds; (5) obesity; (6) a high maternal age; (7) a parity of five or more [12]. Since these high-risk factors may be absent, screening for glucose intolerance during all pregnancies is advisable.

Previous Abnormality of Glucose Tolerance

Individuals who have had documented hyperglycemia and have subsequently returned to normal glucose tolerance fit in the category of previous abnormality of glucose tolerance. Situations that may unmask a predisposition to glucose intolerance include pregnancy, the acute phase of a myocardial infarction, serious trauma, and ingestion of certain diabetogenic medications (Table 1-1).

Potential Abnormality of Glucose Tolerance

Individuals in the category of potential abnormality of glucose tolerance have not been shown to have abnormal glucose tolerance previously, but they are at an increased risk over the general population for the develop-

ment of diabetes. Those who have a monozygotic twin or other first-degree relative—sibling, parent, offspring—with either type I or type II diabetes fall into this category. Persons who are obese and mothers who have delivered babies weighing more than 9 pounds also fall into this category.

DIAGNOSTIC METHODS

Tests Used for Making the Diagnosis of Diabetes

FASTING PLASMA GLUCOSE. The initial laboratory assessment for the diagnosis of glucose intolerance in adults is the fasting plasma glucose. The blood sample should be obtained in the morning, 10 to 16 hours after fasting, before noncaloric stimulants, that is, coffee and tea, are ingested and before any smoking activities. In nonpregnant adults, the demonstration on two separate occasions of a fasting plasma glucose of 140 mg/dl or greater is enough evidence to make the diagnosis of diabetes mellitus. Values of less than 115 mg/dl are considered normal. If the value is between 115 and 140 mg/dl or there are other clinical indications of diabetes, an oral glucose tolerance test is in order. Glucose values obtained from whole blood rather than plasma are approximately 15% lower, so the fasting criterion would be 120 mg/dl.

ORAL GLUCOSE TOLERANCE TEST. The oral glucose tolerance test (OGTT) should be performed in the morning. Before testing the patient must fast for 10 to 16 hours, following a period of at least 3 days of unrestricted diet containing at least 150 gm of carbohydrate per day, and during this period normal exercise should be encouraged. Also, as shown in Table 1-1, many drugs are known to influence glucose tolerance. When possible, these drugs should be discontinued for at least 3 days prior to the OGTT. It should be recognized that certain drugs are known to interfere with various laboratory tests for serum glucose (see Table 4 of [12]). During the test, the patient should remain seated and should not smoke, drink coffee, or eat food until the test is completed. For nonpregnant adults, a fasting blood sample is collected, and 75 gm of glucose dissolved in no more than 400 cc is ingested over a 5-minute period. Blood samples are collected at 30-minute intervals for 2 hours. As shown in Figure 1-1 (p. 7), a fasting plasma glucose of less than 140 mg/dl coupled with a 2-hour value of 200 mg/dl or more is diagnostic of diabetes mellitus, providing at least one value between ½ and 1½ hours is equal to or greater than 200 mg/dl. The diagnosis should not be made unless the above criteria are present on two separate occasions.

The diagnosis of impaired glucose tolerance in nonpregnant adults is indicated when the fasting value is less than 140 mg/dl and the 2-hour value during an OGTT is between 140 and 200 mg/dl. Intervening values during the glucose tolerance test must be greater than or equal to 200