Applied Biochemistry of Clinical Disorders

ALLAN G. GORNALI

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EDITED BY

Allan G. Gornall PH.D., D.SC., F.R.S.C.

Professor of Clinical Biochemistry
University of Toronto, Toronto, Ontario, Canada

with 25 contributors and 132 illustrations

The authors and publishers have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indictions and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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This book is dedicated
to the vision of a
Chair in Clinical Biochemistry
in the
Faculty of Medicine
of all major Universities

Contributors

LYNN C. ALLEN, Ph.D., D.Cl.Chem.
Chapter 22
Assistant Biochemist, Department of Clinical Biochemistry, Toronto General Hospital; Assistant Professor, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

KENNING M. ANDERSON, M.D., Ph.D., F.R.C.P.(C)
Chapter 24
Associate Professor, Departments of Biochemistry and Medicine, Rush Medical College, Chicago, Illinois

ANDREW DeWITT BAINES, M.D., Ph.D.
Chapter 7
Professor, Departments of Clinical Biochemistry and Medicine, University of Toronto, Toronto, Ontario

BHAGU R. BHAVNANI, Ph.D.
Chapter 13
Associate Professor, Department of Obstetrics and Gynecology, McMaster University Health Services Center, Hamilton, Ontario

PHILIP D. BONOMI, M.D.
Chapter 24
Assistant Professor, Department of Internal Medicine, Rush Medical College, Chicago, Illinois

W. CARL BRECKENRIDGE, Ph.D.
Chapter 18
Associate Professor, Department of Biochemistry, Dalhousie University, Halifax, Nova Scotia

PETER J. BRUECKNER, M.D., C.M., F.R.C.P.(C)
Chapter 5
Staff Biochemist, Department of Biochemistry, Sunnybrook Medical Center, Assistant Professor, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

JEREMY J. CLAPP, Ph.D.
Chapter 15
Clinical Chemist, Department of Clinical Biochemistry, Mount Sinai Hospital; Assistant Professor, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

STANISLAW DUBISKI, M.D., Ph.D.
Chapter 4
Professor, Departments of Medical Genetics and Clinical Biochemistry, and Member, Institute of Immunology, University of Toronto, Toronto, Ontario

DAVID M. GOLDBERG, M.D., Ph.D., F.R.I.C., F.R.C. Path.
Chapters 3 and 10
Biochemist-in-Chief, Department of Biochemistry, The Hospital for Sick Children; Professor and Chairman, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

ALLAN G. GORNALL, Ph.D., D.Sc., F.R.S.C.
Chapters 1, 9, 10, and 13
Professor, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

JAMES A. HEININGER, Ph.D., D.Cl.Chem.
Chapter 16
Assistant Biochemist, Department of Biochemistry, The Hospital for Sick Children; Lecturer, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

J. GILBERT HILL, M.D., Ph.D.
Chapter 19
Head, Service Division, Department of Biochemistry, The Hospital for Sick Children; Associate Professor, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

JOSEPH B. HOUPT, M.D., F.R.C.P.(C)
Chapter 12
Director, Trihospital Rheumatic Disease Unit, Mount Sinai Hospital; Associate Professor, Department of Medicine, University of Toronto, Toronto, Ontario

JOHN A. KELLEN, M.D., Ph.D., F.R.C.P.(C)
Chapter 14
Professor, Department of Clinical Biochemistry, University of Toronto; Staff Physician, Sunnybrook Medical Center, Toronto, Ontario

CHOONG-CHIN LIEW, Ph.D.
Chapter 25
Professor, Departments of Clinical Biochemistry and Medicine, University of Toronto, Toronto, Ontario

ALLAN W. LUXTON, M.D., F.R.C.P.(C)
Chapter 13
Department of Laboratories, Clinical Chemistry Section, Henderson General Hospital, Hamilton, Ontario

MICHAEL D. D. McNEELY, M.D., F.R.C.P.(C)
Chapters 16 and 20
Medical Biochemist, Island Medical Laboratories, Victoria, British Columbia

ROBERT L. PATTEN, M.D., C.M., F.R.C.P.(C)
Chapters 8 and 18
Clinical Biochemist-in-Chief, Department of Clinical Biochemistry, Saint Michael's Hospital; Associate Professor, Department of Clinical Biochemistry, and Professor, Department of Medicine, University of Toronto, Toronto, Ontario

ALAN POLLARD, M.R.C.P., F.R.C. Path
Chapter 17
Head, Division of Clinical Biochemistry, Department of Laboratories, Mount Sinai Hospital; Associate Professor, Departments of Clinical Biochemistry and Medicine, University of Toronto, Toronto, Ontario

FRANK H. SIMS, M.B.Ch.B., Ph.D.
Chapter 2
Associate Professor (retired), Departments of Pathology and Clinical Biochemistry, University of Toronto, Toronto, Ontario

W. H. CHRIS WALKER, M.B., F.R.C. Path., F.R.C.P.(C)
Chapter 11
Head, Clinical Chemistry Service, and Professor, Department of Pathology, McMaster University Medical Center, Hamilton, Ontario

JOHN R. WHERRETT, M.D., C.M., Ph.D., F.R.C.P.(C)
Chapter 23
Head, Division of Neurology, Department of Medicine, Toronto General Hospital; Professor of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario

COLIN R. WOOLF, M.D., F.R.C.P.(C), F.R.C.P.(Lon.)
Chapter 6
Professor, Department of Medicine, and Director of Postgraduate Training Programs, University of Toronto; Senior Staff Physician, Department of Medicine, Toronto General Hospital, Toronto, Canada

LEEBERT A. WRIGHT, Ph.D.
Chapter 21
Director, Department of Clinical Biochemistry, The Wellesley Hospital; Associate Professor, Department of Clinical Biochemistry, University of Toronto, Toronto, Ontario

Preface

The Clinical Chemistry Laboratory Service is the practical expression of all that we know about the biochemistry of human diseases. The limited usefulness of this service has been due largely to the fact that neither the principles underlying the selection of laboratory tests, nor the interpretation of laboratory data, have been properly taught or understood. Complex and difficult problems have arisen as a byproduct of the effort to make effective use of the resources of analytical chemistry in support of the practice of medicine. These problems involve hospitals, universities, public and private laboratories, health professionals, and government, but the cost-effectiveness of all health services becomes ultimately a concern of the whole community.

This book addresses several aspects of these problems, and the incentive to edit such a volume came from different sources. There have been recurring requests for copies of the lecture synopses provided to students in our course in Clinical Biochemistry. Curriculum revisions have left medical students in many centers with a less-than-coherent account of the biochemistry of human diseases and the role of the laboratory in clinical decision making. Clinicians have shown an interest in updating their knowledge in this area. Clinical biochemists have come to recognize that at the core of their discipline is an understanding of the extent to which each test is sensitive (positive in disease) and specific (negative in health). They must be qualified to comment on the predictive value of the data they provide and to contribute to the continuing education of the practicing physician.

Based on our experience in the field, we present here a practical, systematic account of the biochemistry of human diseases. An effort has been made to steer a course between the Scylla of being superficial and the Charybdis of too much controversial detail. Each chapter has a reading list to facilitate further study. Literature references to support individual statements have been omitted, but can be obtained from the authors. An effort has been made to survey all the common, or particularly interesting, disorders in which biochemical changes contribute to an explanation of the clinical findings and pathologic changes. Special attention has been given to the potential value of laboratory data in understanding the disorder, confirming a diagnosis, monitoring treatment and making a prognosis. North America is in a transition period in the methods of reporting laboratory results. Looking to the future, most reference ranges have been expressed in système international (S.I.) units, with current terminology in parentheses.

The aim has been to create a better understanding of factors that govern the information gained from laboratory tests. The clinician and clinical chemist together must determine the extent to which each test is *sensitive* and *specific*. The clinician should reach a provisional diagnosis, which increases the *preva-*

lence of the suspected disorder to an acceptable statistical level. In situations of *low* prevalence specificity is more important, since the objective is to rule out the presence of disease. In situations of *higher* prevalence sensitivity assumes importance, since the objective is to establish that the patient has the suspected disease. The close relationship between prevalence and the *predictive value* of laboratory tests must become a natural component of our reasoning. A number of *algorithms* are included as a guide to reaching an appropriate decision in a minimum number of steps with a high degree of precision.

Finally, there has been a modest attempt to direct our attention to an obligation that should challenge all health professionals. We must continually question current practice, insist on adequate justification for the use of our technical skills, and establish a means of measuring with reasonable accuracy the benefits of what we accomplish in terms of the demands made on the economy.

Allan G. Gornall
Toronto, Ontario

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M. HEATHER BRYAN, M.D., F.R.C.P.(C)
Staff Pediatrician, Department of Perinatology, The Hospital for Sick Children, Toronto, Ontario

GERARD N. BURROW, M.D., F.A.C.P., F.R.C.P.(C)
Professor, Departments of Medicine, Obstetrics and Gynecology, and Banting and Best Department of Medical Research, University of Toronto; Director, Division of Endocrinology and Metabolism, Toronto General Hospital, Toronto, Ontario

TERRENCE A. DORAN, M.D., F.R.C.S.(C)
Associate Professor, Department of Obstetrics and Gynecology, University of Toronto; Associate Professor, Department of Obstetrics and Gynecology, Toronto General Hospital, Toronto, Ontario

MURRAY M. FISHER, M.D., Ph.D., F.R.C.P.(C)
Associate Professor, Department of Medicine and Department of Pathology; Head, Division of Gastroenterology, Sunnybrook Medical Center, University of Toronto, Toronto, Ontario

CHARLES H. HOLLENBERG, M.D., F.R.C.P.(C), F.A.C.P.
Professor and Chairman, Department of Medicine, University of Toronto; Physician-in-Chief, Toronto General Hospital, Toronto, Ontario

MICHEL KLEIN, M.D., M.Sc.
Assistant Professor, Department of Pathology, University of Toronto; Director, Immunology Laboratory, Toronto Western Hospital, Toronto, Ontario

AARON MALKIN, M.D., Ph.D., F.R.C.P.(C)
Professor and Head, Department of Clinical Biochemistry, Sunnybrook Medical Center, University of Toronto, Toronto, Ontario

J. GERALD SCOTT, M.D., F.R.C.P.(C), F.A.C.P.
Associate Professor, Department of Medicine, University of Toronto; Senior Physician, Toronto General Hospital, Toronto, Ontario

EVAN R. SMITH, M.B., F.R.A.C.P.
Assistant Professor, Department of Medicine, McMaster University Medical Center, Hamilton, Ontario

DONALD J. A. SUTHERLAND, M.D., Ph.D., F.R.C.P.(C)
Assistant Professor, Department of Medicine, Sunnybrook Medical Center, University of Toronto, Toronto, Ontario

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Contents

PART ONE

GENERAL TOPICS

1

Basic Concepts in Laboratory Investigation

Allan G. Gornall

"Medicine is a science of uncertainty and an art of probability. One of the chief reasons for this uncertainty is the increasing variability of the manifestations of any one disease."
—Osler

HEALTH AND DISEASE

People usually seek the help of a physician because of some discomfort or dis-ease. On average, about 80% of the population experiences some form of illness during any one year. What is it that distinguishes health from disease? An abnormality noted or suspected by a patient is called a *symptom* (e.g., dizziness, pain, cough, diarrhea). An abnormality observed by the physician is called a *sign*. Signs include information obtained by inspection (*e.g.*, edema of the ankles, jaundiced sclera), by palpation (*e.g.*, enlarged liver, a lump in the breast), by percussion (*e.g.*, fluid in the lung or abdomen), and by auscultation (*e.g.*, heart sounds, wheezy breathing). Patients may suspect that they have an illness and complain of real or imagined symptoms. A medical investigation may reveal no detectable disease and the patient may be 'cured' by effective reassurance. Alternatively, people may believe that they are free of any symptoms of ill-health and yet be found at a routine examination to have early signs of serious disease.

A ***disease*** is a composite of signs and symptoms associated with a specific pathologic process. Some disease states are relatively easy to identify because there are observable *lesions* (*e.g.*, measles). In other cases only the consequences of the disorder are observed, the lesion perhaps being a genetic defect involving a single amino acid in a protein (*e.g.*, sickle cell anemia). Most diseases have a known cause or *etiology*, but some illnesses cannot be proved to be due to any known cause. When an abnormality is observed but the cause is unknown it is described as *idiopathic;* when function is disturbed but no organic cause can be found (*e.g.*, when an abnormality is believed to be psychosomatic) it is often called *functional*. The *pathogenesis* of a disease is a description of the factors involved in its development. The definitive diagnosis of a disease usually requires objective evidence of the pathologic process, such as isolating a bacillus or virus, demonstrating a specific biochemical abnormality, visualizing a kidney stone by x-ray, seeing evidence of myocardial infarction on an electrocardiogram, finding an inflamed appendix at surgery, or locating a lesion in the tissues by biopsy or at autopsy. Sometimes a disease may be difficult to define, or have more than one cause; the combination of symptoms, signs, and lesions may then be referred to as a *syndrome*.

The problem of distinguishing between health and disease depends on a concept of what is ***normal.*** There are many definitions of normal but in relation

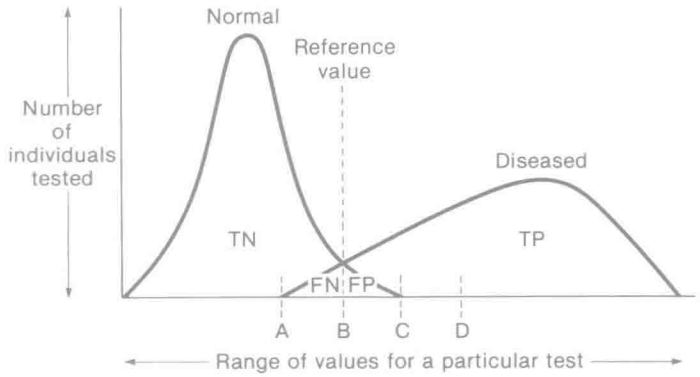

FIG. 1–1. Hypothetic distribution of laboratory values for a particular biochemical test in 'normal' and 'diseased' populations. TN = True negative; TP = true positive; FN = false negative; FP = false positive. A, B, C, and D are decision points (or reference values) referred to in the text.

to health the choice lies between trying to define an 'ideal' state, which is difficult, or determining an 'average' state in people considered to be healthy. In terms of a particular biochemical parameter the latter method results in a more or less symmetric (Gaussian) distribution about a mean, producing the familiar bell-shaped curve. *Statistical theory* then defines, at two standard deviations (±2 SD), the limits within which 95% of the examined population will lie. This should encompass variations due to analytic, biologic, demographic, and environmental factors. A population having a specific disease will usually have an asymmetric (nonparametric) distribution, which in most cases overlaps the 'normal' bell curve (Fig. 1–1). Because of this asymmetry the frequency distributions of laboratory results in both normal and diseased populations can be listed in ranked order and decision lines drawn as the 2.5 and 97.5 percentiles.

DIAGNOSIS AND THE VALUE OF LABORATORY TESTS

In coming to a diagnostic decision most clinicians appear to follow a recognized system (Fig. 1–2). Initial hypotheses are formulated from memory (experience) as soon as the patient has been questioned and examined. These hypotheses can be tested in various ways, including the acquisition and perusal of laboratory data. New information may lead to new hypotheses, which are 'recycled' several times, if necessary, until reduced to a diagnostic decision on which action can be taken. The patient's response to therapy may lead to clinical improvement, or to new developments which may require the consideration of new hypotheses.

When a specific diagnostic problem can be identified (*e.g.*, hypercalcemia, hyponatremia, etc.), the physician may switch to a tree-branching type of approach (see, for example, Fig. 5–3). Such diagnostic ***algorithms*** can assist the physician in reaching an appropriate decision in a minimum number of steps with a high degree of confidence. The diagnostic process is thus one of garnering information until, ideally, the probability of the disease approaches 100%, but in practice this is often much lower before a decision has to be made.

How can one assess the *efficiency* of a biochemical test in discriminating between the presence and absence of disease? The value of a laboratory procedure is measured in terms of the information gained, which depends on the following factors:

FIG. 1–2. The hypotheticodeductive process of reaching a diagnosis or a decision. (Modified from Fabb WE *et al* (eds.) Focus on Learning In Family Practice. Melbourne, Australia, Royal Australian College of General Practitioners, 1975)