6th EDITION

Larone's MEDICALLY IMPORTANT FUNGI

A GUIDE TO IDENTIFICATION

Thomas H. Walsh
Randall T. Hayden
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Cover: *Aspergillus fumigatus* on Sabouraud dextrose agar at 30°C for 4 days. Green velvety colony with a narrow white border. Microscopic structures consisting of septate hyphae and unbranched conidiophores with enlarged vesicle at the top. Compact uniseriate phialides bearing chains of round conidia only on the upper two-thirds of the vesicle. See pp. 295 and 450.

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Dedicated with love
To Ronit
Jessie
Beth
and with loving memory
to John D. Lawrence

Dedicated with love
To Laura, Emma, John, Frances, and Margaret Walsh

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Preface to the Sixth Edition

Each edition of this book has been written with the intention of making the identification of clinically encountered fungi a more logical, understandable, and enjoyable endeavor for the personnel of clinical mycology laboratories as well as for others with an interest in the field. The accompanying goal is to broaden the reader's knowledge and provide current information regarding emerging and established fungal pathogens as well as new methods that can be applied in clinical laboratories. To those ends, the original format that has proved to be so successful is carefully maintained in this edition while additions and updates have been made throughout the book.

This new edition represents a passing of the torch of writing this esteemed, beloved, and time-honored book by Dr. Davise H. Larone to Dr. Thomas J. Walsh and Dr. Randall T. Hayden. Tom, Randy, and Davise worked with extraordinarily close synergy in providing seamless continuity in order to update this important laboratory diagnostic resource in medical mycology.

The majority of recent advances in our field have been based on molecular taxonomic studies applied to the medically important fungi. This continues to result in a molecular labyrinth of taxonomy and nomenclature adjustments. Phylogenetic (evolutionary development) studies continue to discover that organisms which may appear morphologically identical and that have been thought to be a single species are instead a species complex (a collection of related but distinct species). The "new" individual species may possess unfamiliar names. Moreover, these studies also are revealing that organisms thought to be within one genus or order now need to be transferred to another phylogenetic category that allows for a more accurate classification but leads to a change in nomenclature.

Since these changes may be confusing, we have endeavored to provide continuity with earlier names and nomenclatural stability

in areas of uncertainty. Nonetheless, over time, eventual accumulation of data regarding the distribution, clinical relevance, and antifungal susceptibility of newly described fungal species may lead to improved diagnosis and treatment of our patients. Recognizing the rapid changes that are occurring in terminology, we have introduced a discussion on taxonomy and nomenclature in order to help guide the reader through the substantial changes that are occurring in this area of medical mycology. The "Taxonomy and Nomenclature" essay in the Basics section outlines the principle of "one fungus/one name" and the consequences of simplifying, or in some instances complicating, the nomenclature. We note the transition of some common *Candida* species to the less commonly known teleomorph names, and exemplify cases of "cryptic species" that may only be identified by molecular tools.

The companion offshoot of molecular studies is the expanded variety of methods developed for the identification of fungi. As these methods are escalating in availability and usage, especially in reference laboratories, Part III, "Basics of Molecular Methods for Fungal Identification," has been updated in this edition. This section is not an instruction on performing molecular assays; instead, its aim is to provide basic information to increase familiarity, comprehension, and comfort with the terminology, principles, and literature involved. It is written with the goal of increasing familiarity with the methods of molecular identification, especially for those readers who have traditionally relied on morphology and biochemicals to determine the identification of clinical isolates. Availability of morphological assessment, biochemical reactions, and molecular methods will allow the use of whichever systems are appropriate under the particular circumstance. We discuss several new technological advances that have become available since the last edition. Several commercial systems have incorporated real-time PCR and melt curve analysis in an integrated platform. Next-generation sequencing (NGS) is being incorporated into several new platforms that will likely be used increasingly in laboratory diagnostic mycology. The T2 system, which employs PCR and magnetic resonance technology, has the ability to rapidly detect five leading *Candida* spp. directly from blood.

This edition also includes descriptions of new emerging pathogens, such as *Candida auris* and *Aspergillus tanneri*. Detailed footnotes of nomenclatural changes that may be ongoing, but are not fully validated or routinely used in clinical laboratories, are now provided. Of particular note is the substantial increase in detailed descriptions of the epidemiological, clinical, and antifungal susceptibility characteristics of each organism. We also have revised the references throughout the book, adding many more primary references as well as updated atlases for resources. The section on reagents and biochemicals has been extensively reviewed to assure that all contact information, including websites, is most current.

Suggested readings for further information on each organism are still a standard component of each page in Part II. As new books and many valuable journal articles have been published in recent years, they have replaced some of the old, standard texts that many of us have used for a long time. In some instances, the older texts are still listed; this is because they contain a wealth of classic information that is not often covered as completely in the newer texts. However, the old nomenclature in these classic texts needs to be evaluated carefully to ensure correct interpretation relative to the more recent nomenclature.

Each edition of this book has been written with the needs of the reader foremost in mind. We strive to serve the clinical mycology community and their patients with this book as a key resource for laboratory diagnosis of medically important fungi. Throughout the years, many readers have offered helpful suggestions and requests that have been taken to heart and implemented toward the enhancement of the book. Such input plays a large role in ensuring that the goals of the book will be met; it is therefore most sincerely appreciated and we hope that it will continue.

March, 2018

Preface to the First Edition

More than ever, clinical laboratory personnel with limited experience in mycology must culture and identify fungi isolated from clinical specimens. Even after attending a course in the subject, technologists often need guidance in identifying the great variety of organisms encountered in the lab. With the advent of proficiency testing by local and national organizations, technologists have a need and opportunity to practice and increase their skills in the medical mycology laboratory.

Most classic texts, though rich in information, are arranged according to the clinical description of the infection; the textual discussion of any particular fungus can be located only from the index or table of contents. Since the technologist doesn't know the name of an unidentified fungus and usually has little or no knowledge of the clinical picture, these texts are at best difficult to use effectively. The unfortunate result is the all-too-common practice of flipping through an entire mycology textbook in search of a picture that resembles the organism under examination. Such a practice may make the more accomplished mycologist's hair stand on end, but it is a fact to be acknowledged.

This guide is not meant to compete with these large texts, but to complement them. The material here is so arranged that the technician can systematically reach a possible identification knowing only the macro- and microscopic morphology of an isolated organism. Reference can then be made to one of the classic texts for confirmation and detailed information.

Many possible variants of organisms are found under several categories of morphology and pigment. The outstanding characteristics are listed on the page(s) apportioned to each organism, and references are suggested for further information and confirmation (see How To Use the Guide).

Medically Important Fungi avoids the jargon so commonly and confusingly used in most mycology books. Drawings are used wherever possible to illustrate organisms described in the text. To ensure clarity, a glossary of terms is included, as well as a section on laboratory techniques for observing proper morphology. Another section includes use of the various media, stains, and tests mentioned in the book.

The actinomycetes, although now known to be bacteria rather than fungi, are included because they are frequently handled in the mycology section of the clinical laboratory.

It is believed that this guide will enable students and medical technologists to culture and identify fungi with greater ease and competency and in so doing to develop an appreciation of the truly beautiful microscopic forms encountered.

I wish to acknowledge with gratitude the encouragement and advice received from my co-workers at Lenox Hill Hospital, and Dr. Norman Goodman, Mr. Gerald Krefetz, Mr. Bill Rosenzweig, Ms. Eve Rothenberg, Dr. Guenther Stotzky, Mr. Martin Weisburd, Dr. Irene Weitzman, and Dr. Marion E. Wilson.

New York
December, 1975

Acknowledgments

With the writing of this new edition, we are grateful for the willingness of so many in our field to help in numerous ways. Our everlasting gratitude is also extended to the many colleagues who assisted in the preparation of previous editions; most of their contributions are now substantive and integral parts of the ongoing Guide.

Dr. Sanchita Das from North Shore University Hospital, Evanston, IL, generously contributed her time and expertise to update the section entitled "Basics of Molecular Methods for Fungal Identification" (Part III) which she had originally written for the 5th edition.

Our colleagues in Dr. Francis Barany's molecular microbiology research laboratory at Weill Cornell Medicine have been extremely helpful and supportive during the writing of this edition as well as the previous edition.

Dr. Stephen Jenkins, Director of the Clinical Microbiology Laboratory of the NewYork–Presbyterian Hospital/Weill Cornell Medicine (NYPH/WCM) has always readily offered valuable advice and been very supportive. Dr. Lars Westblade, Associate Director of the Clinical Microbiology Laboratory, contributed numerous helpful suggestions for additions to this edition. As noted in previous editions, almost all the organisms shown microscopically and/or as cultured colonies were prepared in the Mycology Laboratory of NYPH/WCM. We will forever be indebted to the staff of the mycology lab for their enormously significant contributions over the years.

Pat Kuharic of the Photography Department of Weill Cornell Medicine has given us the benefit of her outstanding expertise in preparing the excellent color photographs of fungal colonies as well as the black and white photomicrographs. With her talent and professional passion to get it "just right," she is a great asset to the book.

Aleina Zehra, administrative assistant to Dr. Walsh, meticulously reviewed and updated the many Internet websites and suppliers'

locations mentioned throughout the book, as well as assisting in the preparation of working manuscript drafts of various sections.

We thank the staff of the St. Jude Children's Research Hospital, Department of Environmental Health and Safety, for their assistance in reviewing the section related to packaging and shipping of hazardous materials.

Dr. Sybren de Hoog kindly provided a 2-year subscription to the *Atlas of Clinical Fungi*. Drs. David Warnock and Michael Pfaller discussed perspectives with us on fungal taxonomy and nomenclature.

Last, but definitely not least, we extend our deep appreciation to the members of ASM Press. Christine Charlip, Director, has been highly supportive of this 6th edition as an important contribution to ASM Press's library of clinical microbiological resources. Kudos also goes to Larry Klein, Production Manager; Ellie Tupper, Senior Production Editor; and the marvelous associates who contributed to the production of this edition: Mark Via, copyeditor; Susan Schmidler, interior design; and Debra Naylor, cover design. They have been extremely helpful, creative, flexible, and patient and are much appreciated.

A NOTE FROM DR. LARONE

It has been my great honor, and a source of enormous satisfaction, to have written the first five editions of *Medically Important Fungi: A Guide to Identification* as sole author. I realized, after the 5th edition, that it would be wise to have some colleagues join me in writing the next editions. I can't thank Tom Walsh and Randy Hayden enough for agreeing to take on that endeavor. Enormous appreciation also goes to Sanchita Das for working so closely with me to create the Molecular section in the 5th edition and updating it with us in the 6th edition.

My greatest continuous long-standing appreciation goes to Ellie Tupper, who for the 4th through 6th editions has been production editor and watchful overseer, always working very closely with me and ensuring the beautiful production and high quality of the book. I have often said, and most truly mean it, that her name, along with ours, deserves to be on the cover of the book, not just on this page.

Ellie: I, the coauthors, and all the readers owe you an enormous "Thank You" and look forward to your remaining our very talented and essential partner and guide.

About the Authors

Thomas J. Walsh, MD, PhD (hon), FIDSA, FAAM, FECMM, serves as Professor of Medicine, Pediatrics, and Microbiology & Immunology at Weill Cornell Medicine of Cornell University; founding Director of the Transplantation-Oncology Infectious Diseases Program and the Infectious Diseases Translational Research Laboratory, Henry Schueler Foundation Scholar in Mucormycosis; Investigator of Emerging Infectious Diseases of the Save Our Sick Kids Foundation; and Attending Physician at the NewYork–Presbyterian Hospital and Hospital for Special Surgery. Dr. Walsh directs a combined clinical and laboratory research program dedicated to improving the lives and care of immunocompromised children and adults with invasive mycoses and other life-threatening infections. The objective of the Program's translational research is to develop new strategies for laboratory diagnosis, treatment, and prevention of life-threatening invasive mycoses in immunocompromised patients. Dr. Walsh brings to this book more than three decades of experience in the field of medical mycology, with clinical and laboratory expertise across a wide spectrum of medically important fungi and mycoses. In addition to patient care and translational research, Dr. Walsh has also mentored more than 180 students, fellows, and faculty, many of whom are distinguished leaders in the field of medical mycology throughout the world.

Randall T. Hayden, MD, is Director of Clinical Pathology Laboratories and Director of Clinical and Molecular Microbiology and Member in the Department of Pathology at St. Jude Children's Research Hospital in Memphis, Tennessee. He joined the faculty there in 2000, following postdoctoral training in microbiology and molecular microbiology at the Mayo Clinic and in surgical pathology at the MD Anderson Cancer Center. He is board certified in Anatomic and Clinical Pathology with sub-specialty certification in Medical Microbiology. His research interests focus on the application of molecular methods to diagnostic challenges in clinical microbiology, with particular emphasis on the diagnosis of infections in the immunocompromised host. He is editor-in-chief of *Diagnostic Microbiology of the Immunocompromised Host*, 2nd Edition; co-editor of *Molecular Microbiology, Diagnostic Principles and Practice*, 3rd Edition; and section editor for the *Manual of Clinical Microbiology*, 12th Edition, all from ASM Press.

Davise H. Larone is Professor Emerita at Weill Cornell Medicine in the Department of Pathology and Laboratory Medicine and the Department of Clinical Microbiology and Immunology. From 1997 to 2008, she served as Director of the Clinical Microbiology Laboratories of The NewYork–Presbyterian Hospital, Weill Cornell Center. Prior to that, she was for many years at Lenox Hill Hospital, New York, rising from technologist to Chief of Microbiology. During that period, in 1985, she received her PhD in Biology/Microbiology from New York University. Her interest in clinical mycology dates from the 1970s. Her undergraduate degree was in Medical Technology from the University of Louisville, but her love for drawing led her to study art on the side. The combination of her organizational skills and her art background resulted in the first edition of this book in 1976. The subsequent editions in 1987, 1995, 2002, and 2011 all feature Dr. Larone's elegant drawings. Dr. Larone has served on numerous standards, advisory, editorial, educational, and examination boards/committees. Over the years, she has presented more than 100 workshops and lectures in 52 cities in the United States and in 14 cities in nine other countries. She has received numerous awards for teaching and for contributions to clinical mycology.

Basics

How To Use the Guide

Before beginning to use the guide, the reader should understand several points.

Fungi often appear different in living hosts than they do in cultures. Part I (pp. 17–72) is designed as a guide for preliminary identification of fungi seen on direct microscopic examination of clinical specimens.

In Part II (pp. 73–331), the descriptions of the macroscopic and microscopic morphologies of the cultured fungi pertain to those on Sabouraud dextrose agar (SDA) unless otherwise specified. SDA may not be as regularly used for primary isolation of fungi directly from specimens as it was in the past, due to evidence that it is not as supportive as once believed (Scognamiglio et al., 2010). Fortunately, the descriptions can also be applied to growth on alternative media.

Many moulds begin as white mycelial growths, and coloration occurs at the time of conidiation or sporulation. Hence, organisms are listed under their most likely color(s) at maturity, when the typical microscopic reproductive formations are more readily observed.

In Parts I and II, when feasible, organisms are arranged in an order based on morphologic similarities (rather than alphabetical order) to facilitate convenient comparison.

This book is a *guide to identification*. Standard texts and our suggested references should be used for additional information concerning clinical disease, history, ecology, immunology, and therapy.

As molecular assays are increasingly being employed for identification of fungi, the basics of these methods and their utility in the clinical mycology laboratory are discussed in Part III (pp. 333–357).

Instructions for general laboratory procedures, i.e., collection of specimens, direct microscopic preparations, primary isolation, slide cultures, special tests, maintenance of stock cultures, and the like, are