

Middleton's Allergy: Principles and Practice, 6th edition, 2 volumes. N Franklin Adkinson Jr MD, John W Yunginger MD, William W Busse MD, Bruce S Bochner MD, Stephen T Holgate MD DSc, and F Estelle R Simons MD. Philadelphia: Mosby/Elsevier. 2003. Hard cover, illustrated, 1,764 pages, with indexes and CD ROM, \$275.

Middleton's Allergy: Principles and Practice is considered the "bible" of the discipline. It is the most complete magnum opus in the field. Its list of authors is a "who's who" of allergy and immunology, with 165 contributors from 8 countries. Ninety-four chapters are contained in 2 volumes, with a total of 1,764 pages. In the 6th edition there are 10 new chapters and new authors in 40 of the 94 chapters, injecting "new blood" and reflecting the great recent increase in knowledge about allergy and immunology. Volume 1 is dedicated to the basic sciences and Volume 2 to the clinical aspects.

I will begin my review with a disclaimer. Although in preparation for my allergy boards in 1985 I read an earlier edition from cover to cover, I did not read all the pages of this updated tome. Of the 94 chapters I read only a few completely. However, I did use the book the way most of us use reference books. For example, I read several of the chapters for background on certain topics in preparation for talks on related subjects. I also spot-read certain sections regarding some of my patients' health problems. In preparation for depositions as an expert witness, I reviewed certain parts of the book and also used it as an authoritative text for a legal basis. Some of the tables and figures I have adapted for presentations. For all of these typical uses the book works very well.

The following is a brief perambulation through the text, to illustrate its broad and comprehensive coverage. Volume 1 starts with a succinct, well-written summary of the immune system that presupposes at least a college-level background in immunology and sets the stage for the rest of the volume. The second chapter outlines molecular biology and genetic engineering, including specifics on the newly burgeoning fields of genomics and proteomics. Basic genetics is discussed, followed by more specific infor-

mation on the genetics of allergens and asthma. Immunoglobulin structure and function is detailed, followed by an in-depth discussion of the complement system, which now involves more than 30 proteins. Because of its central role in immediate hypersensitivity, a whole chapter is devoted to the synthesis and regulation of immunoglobulin. Cellular adhesion and the molecules involved in the process of recruiting cells are outlined, including the structure, function, and biochemical characteristics of those molecules. The confusing role of cytokines in the immune response is addressed, followed by a cutting-edge discussion on chemokines, the chemotactic cytokines.

Chapter 12 discusses antigen presentation, including the role of antigen presenting cells and the function of T cells. The following chapters discuss the role of mediators in cell physiology, including mast cell, lipid, and the neurogenic inflammatory mediators. A discussion on white cell physiology follows, including sections on mast cells, basophils, lymphocytes, neutrophils, eosinophils, monocytes, and macrophages. The role of the respiratory epithelial cells and vascular endothelium in the immune response is examined, followed by the biology of airway smooth muscle cells. Chapter 26 summarizes the role of apoptosis (programmed cell death) in the inflammatory response and discusses the death signaling pathways. The basics of cellular immunity are expounded upon, including more on antigen presenting cell function, antigen recognition, the role of the histocompatibility complex expression, and the emergence of cytotoxic T cells, Type I and Type II T-helper cells, and T-suppressor cells and their complex interactive role in the immune response. The numerous cytokines that play a role in the recognition, proliferation, and communication between various cells in the immune response are also covered. With this extensive background on the basics of immunology, the following chapter summarizes allergic inflammation, including the interaction of T-helper cell function and the generation of specific immunoglobulin. The multiplicity of cells involved in the allergic response, as well as the mediators and cell surface receptors involved in the allergic response are examined. The brief chapter

on animal models of asthma illustrates new techniques, including transgenic methodology, gene knockout models, and monoclonal antibody intervention to dissect biologic functions. A plethora of known and potential mediators have been examined in asthma animal experiments.

There is then a summary chapter on the pathophysiology of allergic inflammation, followed by specifics on allergic airway disease. After 514 pages of basic immunology, Section B examines aerobiology and the clinical diagnosis of allergy. It begins with a chapter on air pollution, both outdoors and indoors, followed by an examination of allergens and a discussion of sampling methods. Briefly summarized are the major pollen allergens in the various regions of North America, as well as fungal aeroallergens. Indoor allergens, including dust mites, cockroaches, and animal danders, are explored in detail, as are avoidance measures. The preparation and standardization of allergen extracts are reviewed, followed by a section on the physicochemical and biochemical characteristics of various aeroallergens. In a similar fashion the biology of food allergens is examined. Discussion of the role of laboratory testing for allergic and immunodeficiency diseases follows, then skin testing for the diagnosis of allergies, as well as the pitfalls involved in that technique. Nasal provocation testing and bronchial challenge testing are each given their own chapter.

Chapter 41 begins a new section on physiology, starting with cutaneous immunology, followed by immunologic and nonimmunologic lung defense mechanisms, which examines both normal mechanisms and disease. Airway smooth muscle and the extracellular matrix in normal and diseased lung are also examined. Normal lung development, structure, and physiology are addressed and compared to asthmatic pathophysiology. Airway mucus and its constituents are explored, as well as the role of mucus in asthma. In preparation for the sections on the treatment of asthma is a discussion of aerosols and the delivery systems of drugs that treat airway disease. The anatomy and physiology of the nose and nasal airflow are outlined to pave the way for the subsequent discussion of rhinitic syndromes.

Section D in Volume 1 covers the pharmacology of allergic and respiratory disease, starting with the principles of pharmacotherapeutics, followed by chapters on specific drugs, including β -adrenergic agonists, theophyllines, antihistamines, glucocorticoids, the chromones, antileukotriene, and anti-cholinergic agents. The last chapter in Volume 1 discusses the newer immunomodulating therapeutic agents.

Volume II, Section E, is entirely devoted to the clinical practice of allergy diagnosis and treatment. It starts with the clinical evaluation of cell-mediated immunity, including delayed type hypersensitivity, the role of cell-mediated immunity in autoimmunity, as well as "altered cell-mediated immunity" in gastrointestinal disease (eg, Crohn disease) and endocrine disorders (eg, diabetes). Immune complex diseases and laboratory findings of these syndromes are also examined. The chapter on the primary immunodeficiency diseases reviews the more than one hundred that have been described thus far, and for most the molecular abnormality is described. Clinical evaluation of recurrent infections is outlined, followed by a succinct chapter on human immunodeficiency virus. The role of immunoglobulin in allergic and nonallergic syndromes is discussed, as are eosinophil-related disorders, including allergies, infections, neoplastic disorders, immunologic reactions, and diseases with eosinophil-specific organ involvement. The epidemiology of asthma and allergic disease is followed by a section on the natural history, development, and prevention of allergic disease in childhood. Asthma pathogenesis is examined in the context of genetic, environmental, and immunologic factors. Asthma pathophysiology is then compared to that of chronic obstructive pulmonary disease. The following chapters discuss the differences and similarities in the presentation and management of asthma in infants, children, and adults, and in pregnancy, with emphasis on recent asthma treatment guidelines. A chapter is dedicated to exercise-induced asthma and another to occupational asthma. Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis have their own chapters.

Chapter 76 covers rhinitis, including a detailed discussion of the pathophysiology of allergic rhinitis and a brief discussion of nonallergic rhinitis syndromes. There are also chapters on nasal polyps and the role of fiberoptic endoscopy in the evaluation of

the upper airway. Otitis media is discussed, with emphasis on its association with allergies. Immunotherapy and its physiologic effects are outlined in Chapter 80.

A chapter on diagnosis and treatment of stinging-insect allergy follows, which includes a discussion of immunotherapy for bee stings and the question of when to stop. Natural latex allergy, anaphylaxis and anaphylactoid reactions, and mastocytosis each have their own chapters. Urticaria and angioedema are then covered, with the increasing evidence of an autoimmune role in idiopathic urticaria. This is followed by an examination of atopic dermatitis and the difficulties of managing it. The following sections give an update on the pathogenesis of contact dermatitis (with emphasis on the role of cytokines, T cells, and adhesion molecules) and the diagnosis and treatment of ocular allergies and other immunologic eye diseases.

Food allergies are thoroughly detailed, including the cross-reactivity of food allergens and pollens based on molecular similarities. Food intolerances and the recognized role of non-immunoglobulin E-mediated food hypersensitivity are also covered. The following chapter outlines adverse reactions to food and drug additives and food and drug allergy challenge methods. Adverse reactions to vaccines are addressed, and the authors make it clear that most such adverse reactions are trivial and that the risks from vaccines are generally much less than from the diseases the vaccines prevent. A general overview of drug allergies is presented, including the mechanisms of hypersensitivity. There are chapters on reactions to aspirin and nonsteroidal anti-inflammatories. Last, but not least, is an examination of unconventional theories and unproved methods in allergy, including "environmental illness," "Candida hypersensitivity," and other debunked diagnoses. Unproven diagnostic tests and unproven treatments are also analyzed. Unfortunately "toxic molds," a current controversial diagnosis is not discussed.

If that is not enough to impress the most skeptical Missourian... did I mention the 18,715 references? The obvious question is, who needs this much information? As noted in the book's preface, it is "the most widely owned and referenced authoritative textbook for the discipline of allergy and immunology." Every "self-respecting" allergist or allergy investigator owns a copy. Pulmonary specialists with an interest in immunology

or the upper airway would benefit from access to the book. Respiratory therapists and nurses who are well-grounded in immunology and with intense interest in the field may want it as a reference, but it is not cheap at \$275.

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The Immunological Basis of Asthma. Bart N Lambrecht MD PhD, Henk C Hoogsteden MD PhD, Zuzana Diamant MD PhD, editors. (Lung Biology in Health and Disease series, Volume 172, Claude Lenfant, executive editor.) New York: Marcel Dekker. 2003. Hard cover, illustrated, 800 pages, \$195.

The Immunological Basis of Asthma is a recent volume in the well known "Lung Biology in Health and Disease" series. It is comprehensive (800 pages, 53 authors) and well organized into 4 sections: "The Cells of the Pulmonary Immune Response," "Regulatory Processes in the Pulmonary Immune Response," "Integrated Immunology of Airway Inflammation," and "Immunologic Aspects of Current Asthma Therapy." The primary audience for this book is physicians, especially allergists and pulmonologists interested in respiratory immunology. Only one of the 24 chapters discusses current medications used in asthma therapy, and that chapter focuses primarily on the molecular mechanisms of corticosteroid action—not practical therapeutic information. Most nurses and respiratory therapists are likely to find this book too tangential to their interests. That notwithstanding, the book is well written, well organized, and contains a wealth of information about the immunological mechanisms of asthma.

The first 7 chapters are grouped under the heading "The Cells of the Pulmonary Immune Response" and discuss host defense mechanisms of the lung. There are relatively brief sections on innate immune functions, including mucociliary transport, lactoferrin, lysozyme, complement, epithelial cells, neutrophils, eosinophils, and alveolar macrophages. Each of the subsequent chapters in

this section details a specific cell of the adaptive immune system. The first of these focuses on the critical first step of antigen presentation by dendritic cells and alveolar macrophages to antigen-specific T cells. The next chapter discusses the functions of T lymphocytes, in particular CD4⁺ T cells, in B cell switching to immunoglobulin E production and in the induction of bronchoconstriction. Other chapters provide in-depth discussions of the functions of B cells, mast cells, basophils and eosinophils in the pathophysiology of asthma. The final chapter in this section reviews the immune functions of airway epithelium. This tissue acts not only as a tight physical barrier between the environment and the lung but also as an immunologic organ. Best known are the innate immune functions of ciliary action, mucus production, and immunoglobulin A secretion. However, as this chapter documents, the airway epithelium is also a source of numerous cytokines, chemokines, lipid mediators, growth factors, and reactive oxygen species. Furthermore, asthma can damage the epithelium and alter the phenotype of these cells so that they produce more pro-inflammatory mediators that perpetuate the disease state and may promote airway wall remodeling.

The second section, "Regulatory Processes in the Pulmonary Immune Response," is composed of 6 chapters that have little clinical relevance. The topics include the induction of tolerance and sensitization to inhaled antigens, the polarization of T-helper cells, the regulation of T cells by CD28 and B7 co-stimulatory molecules, the control of lymphocyte trafficking through the lung, and neuroimmune interactions in the pathogenesis of asthma. The chapter in this section that will be of most interest to clinicians is the one that discusses the mechanisms of sensitization to inhaled antigens. Studies are presented regarding inadequate interleukin-12 (IL-12) signaling in the post-natal period by antigen processing cells, leading to deficient Th₁ cell polarization, which is one purported mechanism for the development of atopy and allergic asthma. Also discussed is the importance of timing, route, and dose of allergen exposure in the development of allergy and information about allergen avoidance in early life in preventing allergic disease.

The third section, "Integrated Immunology of Airway Inflammation," is composed of 7 chapters and contains some of the most interesting information in the book. The first

chapter in this section, "Immunopathology of Atopic and Nonatopic Asthma," presents current studies regarding the classic distinction between the intrinsic and extrinsic variants of asthma. In this well written and well illustrated review the authors document that lung tissue from both variants is characterized by increased numbers of activated eosinophils and immunoglobulin-E-positive B cells as well as cells positive for eotaxin, Fe₂R1, IL-4, IL-5, and IL-13. Therefore, despite the distinct differences in clinical presentation between these 2 forms of asthma, they share a common immunopathological mechanism. These findings have led to the intriguing suggestion that intrinsic or nonallergic asthma may be an autoimmune process induced by a virus or another infectious trigger.

The topic of another chapter in this section, "Airway Remodeling as the Outcome of a Chronic Immune Response to Inhaled Allergen," is also of current interest. Recognition that asthma causes permanent loss of lung function is a relatively new concept that has influenced the writers of treatment guidelines to advocate early and continuous anti-inflammatory therapy for all but the most mild asthma. Structural changes in the airways (presumably from recurrent inflammation) include thickening of the reticular basement membrane beneath the luminal epithelium, increases in extracellular matrix molecules (eg, hyaluronan, proteoglycans, and collagens), smooth muscle cell, and mucus gland hyperplasia. This chapter reviews the roles of various cell types in the promotion of the remodeling response, including findings from animal models.

The other chapters in Section 3 cover eosinophilic airway inflammation in a mouse model of asthma, regulation of cellular traffic in the asthmatic lung, cytokine regulation of bronchial hyperresponsiveness, and viral induction of eosinophilic airway inflammation.

The final section, "Immunological Aspects of Asthma Therapy," is composed of 4 chapters, the first of which reviews current asthma therapy and discusses the cellular mechanisms of corticosteroid action. There are also short sections on theophylline, antileukotrienes, B₂ agonists, and allergen immunotherapy. The next chapter succinctly reviews available and potential immunomodulators for treating asthma. These therapies are usually reserved for the most severe asthma that

requires maintenance oral corticosteroids or high-dose inhaled corticosteroids. The drugs covered include cyclosporin A, methotrexate, gold salts, troleandomycin, hydroxychloroquine, leukotriene modulators, and intravenous immunoglobulin. There is also a brief section on anti-immunoglobulin-E therapy, which has been Food and Drug Administration-approved since publication of **The Immunological Basis of Asthma**, as well as discussion of anti-cytokine therapy research. The next chapter reviews the conceptual basis and ongoing experiments to employ bacterial DNA sequences (termed immunostimulatory CpG motifs) as a vaccine to treat asthma. The concept is that bacterial products will shift the patient's immunologic profile from a Th₂ to Th₁ pattern and thereby protect against the development or progression of asthma. The chapter reviews the animal and human studies that have employed this technique. The final chapter addresses gene-based therapies that have been proposed for asthma, with emphasis on the use of adenovirus as a vector. For example, the authors propose adenovirus delivery of antisense oligonucleotides against messenger ribonucleic acid or deoxyribonucleic acid for IL-4 or IL-5 or transcription factors to reduce the production of essential mediators of asthmatic inflammation. Genetic therapy for asthma remains an unproven and distant possibility.

Overall, **The Immunological Basis of Asthma** is an attractive, comprehensive volume that is well written and well illustrated. Each chapter is thoroughly referenced: most chapters include at least 50 and some chapters include as many as 400 citations. At the end of the volume there is a very extensive (104 pages) author index that cross-references (by the first author's surname) every reference cited in the book. There is also a good but briefer subject index.

The most obvious shortcoming of the book is content overlap among the chapters. The chapter authors apparently had no knowledge of the content of the other chapters. This led, for example, to 6 chapters having major sections on cytokines and chemokines and 2 chapters related to cellular trafficking through the lung. Accordingly, this book is best used to research a subject by looking at the coverage of that subject in different chapters

and as a means of locating the existing literature on the subject.

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The Allergy and Asthma Cure: A Complete 8-Step Nutritional Program. Fred Pescatore MD MPH. Hoboken, New Jersey: John Wiley & Sons. 2003. Hard cover, 251 pages, \$24.95.

The book is intended for people who suffer from allergies and asthma. It does not directly target health care professionals, but may be useful to them as well. The title of the book is a bit misleading in that it advertises a “cure,” which is unrealistic. The word “cure” also appears several times in the book, including in chapter titles. In several sections, including the introduction, however, the author is more reasonable and acknowledges that his program does not cure allergies and asthma, but that it can help them “decrease significantly the amount of medication they use daily and be able to enjoy aspects of their lives they thought they would have to do without”—a more appropriate and realistic claim.

The book has 15 chapters organized into 4 parts. Part I covers diagnosis and treatment of asthma and allergies and includes guidelines and currently available medications. Part II discusses the author’s vision of and recommendations for a “complementary medical approach” to allergies and asthma, covering food sensitivities, and there is a whole chapter dedicated to the possible role of candida and yeast in allergies. In Part III, which contains Chapters 7–12, the author details his proposed nutritional program for the “cure.” Chapter 7 provides background, Chapter 8 talks about a specific diet for the “healing phase,” Chapter 9 aims at strategies for weight loss, Chapter 10 provides insights into breathing better, Chapter 11 discusses nutritional supplements, and Chapter 12 covers the use of nutritional supplements to treat asthma and allergies. Part IV contains 3 chapters, which give meal plans, recipes, and a resource

guide for general medical as well as “complementary medical” information.

In the first part of the book the author does an excellent job of providing useful background information about asthma diagnosis, treatment, etiologies, and triggers. That information will be very useful to patients who have asthma and allergies and want to better understand these diseases.

Chapter 3 covers the conventional treatment of allergies, including “allergy shots.” Chapter 4 covers the conventional treatment of asthma and includes an excellent overview of the currently available medications and their pros and cons. Chapter 4 also includes brief sections on the National Institutes of Health guidelines for asthma diagnosis and management, over-the-counter medications, and newer therapies being tested. The material in this section is well selected and organized. Most of the statements in this section are factual and based on current understanding, but some sections that present the author’s perspective and are given more weight, we believe, than the average health care professional in the field would give them. For example, we think there is undue emphasis on the role of candida in allergies.

The book lacks illustrations, which would have helped clarify certain of the book’s messages. Also, although most of the stated information is accurate, specific references to the information sources are not given. The index is useful and well organized. Despite the absence of illustrations and lack of citations to appropriate references, patients will find the information in this section accurate and useful.

In the second and third parts of the book the author describes his 8-step program, which he calls a “modern prescription for health.” The program includes proper nutrition, nutritional supplements, and cleaning up environmental allergens. The program is tailored to individuals, depending on whether they are overweight, have allergies, asthma, or any combination of the three. A very helpful feature, in addition to the useful appendix, is that the author summarizes the recommendations at the end of each chapter, making them easy to reference.

Step 1 of the program is to determine the patient’s food sensitivities via food sensitivity tests and to begin diets that eliminate dairy, wheat, corn, and salicylates. Step 2 is more controversial; it deals with candida and yeast, and this section includes an interesting discussion about “leaky gut”—a

hypothesis for which we know of no strong medical or nutritional evidence. Most of this chapter focuses on candidiasis and fungus, and an extensive candida questionnaire is included. Step 3 concerns an allergen and asthma trigger list, and this section provides a useful questionnaire and worksheet to determine what factors contribute to allergy or asthma reactions. Step 4 is the nutritional program, which is divided into a yeast-free diet, with or without weight loss. The “standard American diet” is discussed and the author concludes that that diet is detrimental. There is a discussion about fruit as a source of simple sugar. The given examples of fruit portion sizes seem questionable to us. It seems that some fruits are avoided because of sugar content when it may be more an issue of portion size. Overall, this is a 3–6-month elimination diet in which most foods seem reasonable to avoid except that the allowable grains on a yeast-free diet are restrictive and most people would have difficulty following this aspect of the program. This is a rigorous diet plan and our experience suggests most people would have a hard time sustaining the motivation necessary to follow it.

Step 5 is about weight loss. The author, Fred Pescatore, wrote a book on the subject of weight loss and recommends it for further weight-loss information. The discussion on fish fails to mention the caveat about heavy metals in fish. The no-cheese (because it contains yeast) aspect would be difficult for most people to follow. The recommendation to eliminate tomatoes is questionable as is the focus on counting sugar grams and not total carbohydrate grams in the yeast-free cereal component. Step 6 deals with the re-introduction of eliminated foods—a 16-week process. Steps 7 and 8 are about supplements. This is a highly individualized aspect of the plan. General recommendations are given for each category discussed. Again, there is undue focus on the anti-candida supplements and medications. The book recommends 10,000 international units 3 times a day of Vitamin A, which we believe is worrisome because of possible toxicity. Health care professionals should have substantial reservations regarding unknown information on some of the recommended supplements, such as Quercetin, active hexose correlated compounds (AHCC), pregnenolone, dehydroepiandrosterone (DHEA), licorice root, and grape seed extract.

Part IV gives detailed lists regarding meal plans and specific recipes and provides a medical resource guide. The meal plans and recipes are useful and relatively nutritionally sound. However, it would take a very highly motivated individual to stay on this meal plan. The author also provides a reasonable list of Web sites and addresses for foundations, societies, and institutions that can provide useful information on asthma and allergies. He also provides “complementary medical” information Web sites.

Overall, once you pass its misleading title and the undue emphasis on the role of candida in allergies, this book is an excellent overview for asthma and allergy patients. It provides very useful background information on etiology, diagnosis, and treatment. The basic principles of eliminating environmental irritants, getting exercise, losing weight, and following a low-carbohydrate diet are reasonable. Unfortunately, they are the most difficult lifestyle aspects to change. Almost anyone would have improved health if they followed the book’s advice on those subjects. The rest of the book’s advice should be evaluated on an individual basis, under the care of a licensed professional, especially aspects regarding some food supplements and the treatment of candida.

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20 Common Problems in Respiratory Disorders. William J Hueston MD, editor. (20 Common Problems series, Barry D Weiss MD, series editor). New York: McGraw-Hill. 2002. Soft cover, illustrated, 369 pages, \$45.

At the onset of the influenza epidemic in the winter of 2004, I spent a frustrating half hour searching online medical references for current influenza treatment guidelines, without success. Soon thereafter I settled down to review this book and was delighted to find a well referenced, clear, and directed chapter on influenza, which quickly answered my questions.

My experience in the practice of clinical medicine leads me to agree with the author’s assertion that the 20 most common

problems in respiratory medicine are among the most common presenting patient complaints and are what primary care providers will want to read about. This textbook is an excellent introductory text for primary care providers in training, and a quick reference for those already in practice. Though written primarily for clinicians, respiratory therapists and nurses will probably also find this book useful.

The book is well organized and thoughtfully arranged into 20 chapters and 5 parts. Part 1 focuses on common presenting symptoms and their evaluation. Parts 2 through 5 cover upper respiratory infections, lower respiratory infections, noninfectious acute respiratory diseases, and chronic respiratory diseases and their prevention. This book’s structure is logical and lends to its easy readability. In addition, highlighted and boxed outlines on the first page of each chapter help to make the information more transparent and quickly accessible. Though not advertised as a pediatrics text, most chapters contain sections on special considerations for children. Pediatric drug dosing and vaccine guidelines and dosing are provided in all chapters that provide that information for adults. In addition, Chapter 10 provides a dedicated discussion of the causes of pediatric cough. The chapter first introduces a framework for evaluating pediatric cough, then discusses croup, epiglottitis, bronchiolitis, and pertussis.

The initial section on respiratory symptoms and their evaluation consists of 3 chapters on cough, dyspnea, and pulmonary function testing. As cough and dyspnea are symptoms rather than disease entities, such a beginning may seem overly broad and basic for the more experienced provider and a sacrifice of an opportunity to discuss 3 other common respiratory disorders in more depth. However, these chapters do lay an important foundation for the novice clinician, as cough and dyspnea are common chief complaints with serious and life-threatening diagnostic considerations. The author’s stated aim with these chapters is to offer a guide to the evaluation of these common complaints as well as an approach to pursue when the initial evaluation does not reveal the underlying cause. Each chapter provides a useful discussion of the pathophysiology, workup, and evidence-based treatment of these disorders, and concludes with a clear and succinct algorithmic flow chart.

For example, the chapter on cough briefly discusses the basic cough mechanism and then reviews the differential diagnosis for both acute and chronic cough. Numerous highlighted tables and charts summarize differential diagnoses and emphasize important points, such as red-flag signs and symptoms for potentially life-threatening causes of cough. The chapter includes an especially useful evidence-based review of treatment options for chronic cough.

The chapter on pulmonary function testing is also clearly written, providing important definitions and an introduction to key clinical concepts. The treatment is somewhat superficial, leaving the reader without enough information to interpret the cited studies independently, though a flow diagram at the end of the chapter presents a useful algorithm.

In Part 2 there is a chapter on pharyngitis, which, like the earlier chapters, is symptom-driven rather than focused on a specific disease entity. The result is brief, paragraph-long discussions on selected causes of pharyngitis, followed by a more satisfying discussion of group A streptococcus pharyngitis, which includes a table that highlights the modified Centor Strep score. This chapter may have been better had it focused instead on Group A streptococcus or perhaps mononucleosis, covering those topics in greater depth while limiting the discussion on influenza and rhinovirus, which have their own chapters.

The chapters that focus on specific diseases, including the common cold, sinusitis, otitis media, otitis externa, and influenza, are detailed and well written. The chapter on the common cold provides a lively discussion and literature review on the overuse of antibiotics for this viral illness—an important topic that is echoed in the chapter on acute bronchitis. Appropriate therapeutic alternatives are discussed, with reference to efficacy studies. Herbal and homeopathic options are also described, though not in great detail. The chapter on influenza is remarkable for its clarity and brevity while retaining clinically pertinent details. Tables highlight the characteristics that distinguish influenza from the common cold, differences in presentation by age group, and comparisons of the 4 antiviral agents available for influenza, including cost considerations. The thoughtful use of tables and graphs is consistent throughout these chapters. However, the coverage of clinical points is not as consistent. For example, the chapter on sinus-

itis exhaustively summarizes the various studies in tables but does not provide basic clinical reference tables, such as treatment options and doses.

The book includes a useful chapter on special considerations in geriatric and immunocompromised patients. This chapter is particularly well structured, thoroughly addressing questions that typically arise in the management of respiratory conditions with these patients. Information is provided on differences in presentation, laboratory and radiographic studies, differences in infecting organisms (with an emphasis on epidemiologic risk factors), empirical therapy, and disposition. A useful algorithmic flow diagram is included, though the algorithm may be overly aggressive in its workup: do all patients suspected of having a lower respiratory tract infection need an arterial blood gas analysis as well as a chest radiograph? Obtaining an arterial blood gas sample is painful, and pulse oximetry is often a reasonable alternative. Though the basic approaches outlined in this chapter are adequate, finer points of therapy must be obtained from more detailed references, such as the use of adjunctive corticosteroids for patients severely hypoxic from pneumocystis pneumonia.

Section 4, on noninfectious acute problems, contains 2 brief chapters: one on pulmonary embolism and the other on lung cancer. They provide enough information to understand the basic pathophysiology, terms, and relevant diagnostic studies, but they lack the detail and tables found in prior chapters. In addition, the algorithm for pulmonary embolism emphasizes the use of ventilation/perfusion scans, though spiral tomograms are frequently used nowadays in the initial evaluation. Also, the recently-published clinical prediction rules for deep vein thrombosis and pulmonary embolism are not discussed.

In Part 5, on noninfectious chronic conditions, the book is back to its best form, offering satisfying detail, clinically relevant tables, and pictures of clinical findings on the topics of allergic rhinitis, asthma, and chronic obstructive pulmonary disease. The chapter on immunizations provides information on disease burden, vaccine efficacy, usage guidelines, and adverse reactions, which providers will find invaluable when discussing these vaccines with their patients. The final chapter draws appropriate attention to the health threat of cigarette smoking, which is the leading cause of prevent-

able death in the United States and a contributor to all respiratory ailments.

This book is not without flaws, though they are generally minor. In addition to the shortfalls already noted, the book suffered some internal inconsistencies by allowing different authors to handle the same subjects. For example, a discussion of influenza in the chapter on pharyngitis uses a definition from a review article from 1976 and is somewhat at odds with the information found in the chapter that is specifically about influenza, which used more recent citations.

We highly recommend this book to all health care providers in training, as well as to experienced clinicians and ancillary staff who want a concise reference. The information is generally current, evidence-based, and exceedingly relevant. The book is attractive, well organized, and overall an enjoyable read.

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Chemokines in the Lung. Robert M Strieter MD, Steven L Kunkel PhD, and Theodore J Standiford MD, editors. (Lung Biology in Health and Disease series, Volume 172, Claude Lenfant, executive editor). New York: Marcel Dekker. 2003. Hard cover, illustrated, 399 pages, \$195.

The highly regarded book series Lung Biology in Health and Disease, under the executive editorship of Claude Lenfant, has added a new volume entitled **Chemokines in the Lung**, edited by Robert Strieter, Steven Kunkel, and Theodore Standiford. These outstanding experts have compiled a comprehensive review that is in keeping with the excellence of the series. This volume, like others in the series, will be of interest primarily to investigators and physicians interested in lung cell biology, but some others will find it of interest as it relates to the

roles of chemokines in specific diseases and their potential roles in therapy.

The book has 3 introductory chapters on general characteristics of chemokines, chemokine receptors, and intracellular signaling mechanisms. Two additional interesting chapters discuss the role of chemokines in lymphocyte trafficking and genetic models of chemokine biology in the lung. The remainder of the chapters are devoted to specific conditions and diseases, including asthma, chronic obstructive pulmonary disease, cystic fibrosis, infectious disease, human immunodeficiency virus, acute lung injury, granulomatous lung inflammation, pulmonary fibrosis, lung allograft rejection, lung cancer, and pleural disorders.

Each chapter is written by experts in the field, and each stands alone as an excellent topical disease-oriented review. The primary literature cited is comprehensive and accurately and critically presented, with extensive references for readers interested in more in-depth research. Although there are predominant chemokines in certain diseases, there is considerable overlap in chemokines related to many disease processes, so there is some overlap in discussion of chemokines in the context of specific diseases. Rather than viewing this as a weakness, I think this overlap helps emphasize the complex nature of chemokines and their complex, interacting roles in the pathogenesis of diverse conditions.

One current problem in chemokine biology is the movement away from acronyms that have been commonly used for chemokines, such as MCP-1 (monocyte chemoattractant protein) and IP-10 (interferon- γ inducible protein). A systematic chemokine ligand naming system, which is based on their receptors, was recently adopted, so MCP-1 is now known as CCL2, and IP-10 is CXCL10. By and large the authors and editors dealt with this nomenclature transition effectively by using tables, both terms, and the preferred new systematic name after defining the common acronym.

I found the chapter on lung allograft rejection (by Belperio, Keane, Ross, and Strieter) to exemplify the high quality of the reviews. The authors draw on an extensive literature on skin rejection, cardiac allograft rejection, and renal allograft rejection, and they integrate diverse investigations into a comprehensive overview and relate the findings to acute lung allograft rejection and bronchiolitis obliterans syndrome. Much of the lung allograft data are from human stud-

ies, and translational studies in animal models are original work of the chapter authors. Presented in the broader context of transplantation biology, the importance of the experiments is highlighted and points strongly toward the potential for targeting chemokines and their receptors for therapies.

As stated by the series editor, Dr Lenfant, in his introduction, the volume as a whole, "takes the reader to the forefront of the field of chemokines. . . and opens the door on new research questions and ideas." Accordingly, the reader will probably have an appreciation of chemokines as natural targets for interventions in lung disease.

In summary, **Chemokines in the Lung** continues the excellence in the Lung Biology in Health and Disease series. It will serve as a valuable introduction to chemokines as well as an authoritative reference to the role of chemokines in lung disease.

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Gene Therapy in Lung Disease. Steven M Albelda, editor. (Lung Biology in Health and Disease series, Volume 169, Claude Lenfant, executive editor). New York: Marcel Dekker. 2002. Hard cover, illustrated, 555 pages, \$185.

The National Heart, Lung and Blood Institute at the National Institutes of Health publishes a series entitled Lung Biology in Health and Disease, under the guidance of the institute's director, Dr Claude Lenfant. For each volume Dr Lenfant selects a specific topic and an editor, who solicits contributions from leaders in the field and combines the contributions to make the final product. The goal is to produce a focused review on the most recent research, a thorough and balanced discussion of newer concepts and controversies, and future directions for research. Thus, these monographs are primarily intended for basic scientists and clinical researchers, as updates on the state of research in their field, and for researchers in training as reference tools.

Volume 169 in this series, **Gene Therapy in Lung Disease**, is edited by Steven Albelda. The book begins with an excellent historical overview that gives some fasci-

nating details on early events in gene therapy and important information on public policies about gene therapy clinical trials with humans. However, there is disappointingly little discussion on the events that led up to what many would consider the biggest setback to date—the death of a 19-year-old man in a trial of gene transfer of an adenoviral vector delivered into the liver, intended as therapy for ornithine transcarbamylase deficiency. That death put all human gene therapy trials on hold in the United States and precipitated intense public and government scrutiny of how these trials are conducted. Wivel, the author of the chapter on that subject, describes the important regulatory changes that followed the man's death, but given Wivel's experience in the field, I wished for some discussion on why that tragic event occurred and on what more we scientists can do to protect our research subjects from harm.

The next 4 chapters give extensive details on the major vector systems under development for gene therapy of the lung. The quality of these 4 chapters differs tremendously. For example, Duan, Yue, and Engelhardt's chapter on adeno-associated virus vectors is outstanding: there is an incredible amount of detail and elegant discussion on the problems and limitations of adeno-associated virus vectors, and possible solutions. The chapter gives a balanced view of the advantages and disadvantages of that vector.

In contrast, the chapter on cationic liposome/plasmid deoxyribonucleic complexes as a gene delivery vehicle is far from balanced. For example, much of the data on the liposome component of the complex is devoted to studies that used GL67, a lipid developed by the pharmaceutical company Genzyme. Another example of lack of balance is that the author used as evidence for efficacy of aerosol plasmid/liposome complexes a publication that deals primarily with the pro-inflammatory effect of the Genzyme GL67 lipid in humans. In that study 4 of the 8 cystic fibrosis patients who received an aerosol of a cystic fibrosis transmembrane conductance regulator-encoding plasmid complexed with GL-67 had a "pronounced clinical syndrome of fever (maximum of 39.6°C), myalgia, and arthralgia" (reference 57, Chapter 4). However, Scheule references this publication as a human study that "demonstrated that vector-specific transgene expression" had occurred and therefore sup-

ports the claim of potential efficacy of the GL67 lipid.

This lack of balance is somewhat disturbing, and it may be partially explained by the fact that the chapter author is the scientific director of gene transfer research at Genzyme. There is no disclaimer that the author is a paid employee of the company and therefore has a potential for conflict of interest. It is now standard practice for peer-reviewed medical articles and reports from research seminars to state at the very beginning any relationship (including financial) the scientist has with an industry sponsor, to warn the audience of a potential bias, and such disclaimers should have been included.

I wondered how many of the other chapter authors are paid consultants to pharmaceutical companies and have a financial interest in developing certain vectors and genes treatments for lung disease. Another question is how many of the authors have themselves founded companies based on their discoveries and thus have potential for financial gain if their technology becomes the "most favored?" At this point I must give my disclaimer: I am a liposome researcher and I founded a biotechnology company, the main focus of which is the development of plasmid liposome complexes for genetic therapy to the lungs. And so how balanced will my review of this volume be? That is not a question I can answer, but the reader should at least know my bias and judge accordingly.

Developing a gene therapy requires enormous amounts of money, which, currently, only industry is willing to invest. The collaboration of industry and academia can achieve that balance of translational research (ie, the academician's goal of conducting hypothesis-driven research that has a direct pathway to clinical applications) and drug development (ie, industry's goal of bringing to market an effective and safe therapeutic agent that grabs the market share for a particular disease/indication) that will improve the quality of life for our patients. We just need to be honest about our scientific and fiscal biases.

The next section of the book focuses on using gene transfer as a tool to study lung disease pathogenesis. I was excited at the prospect of reading these chapters, because I envisioned that they would contain much information that was new to me, as this area has not gotten much attention in the gene therapy literature until rather recently. I was not disappointed.

The 3 chapters in this section were well written, informative, and balanced. In these chapters a case is made that transient expression of cytokines and growth factors could give us important information on the biologic and disease roles of those factors. Unfortunately, much of the information in these 3 chapters was repetitive.

Content overlap is a problem throughout the book and it occurs with mind-numbing frequency, as was particularly evident in the book's last section, which is on gene therapy for specific diseases, including gene therapy, cystic fibrosis, cancer of the respiratory system, alpha-1 antitrypsin deficiency, diseases of the pulmonary circulation, acute lung injury, and lung transplantation. The 2 chapters on cancer are outstanding; they are packed with information and provide very thorough and balanced discussions on the challenges of gene therapy for cancer and how those challenges might be addressed. The 3 chapters on cystic fibrosis are informative but exceedingly repetitious; the background information in these chapters is either repetitive or should have been presented many chapters earlier. For example, the basic description of adenoviral vectors, adeno-associated virus vectors, retroviral vectors, and liposomes as gene delivery system are presented in Chapter 12 ("Strategies for Gene Therapy of Cystic Fibrosis"); the basic description of adeno-associated virus vectors is repeated in

Chapter 13 ("Use of Adeno-Associated Virus in the Treatment of Cystic Fibrosis"); and extensive details on liposomes are given in Chapter 14 ("Use of Liposomes in the Treatment of Cystic Fibrosis"). But those gene delivery systems were described extensively in Chapters 2–6. In addition, the clinical description of cystic fibrosis does not need to be repeated in each of these 3 chapters.

These chapters (as with others in this volume) should have been edited to remove the repetition. In many instances the chapter authors do not see each others' manuscripts, so it is up to the series editor to consolidate information and remove repetition, which is time-consuming, but had it been done, the book could easily have been shortened by one quarter and it could have been a much more cohesive and integrated work. It could be argued that the repetition allows one to read only the specific chapter of interest, but that defeats the purpose of this series. Several review articles have appeared in medical journals on the topics in this book (except perhaps for lung transplantation) but the purpose of combining the information in such a book is to make the whole greater than the sum of the parts. Unfortunately, that is not the case here.

Chapter 15, "Delivery of Genes Through the Lung Circulation," is one of the best in the book. It is short, succinct, and provides much new information. The next 3 chapters (on alpha-1 antitrypsin de-

ficiency, acute lung injury, and lung transplantation) each have extension sections on the basic description of viral and non-viral vectors—all of which should have been eliminated. Each of these chapters includes introductory comments on the disease of interest and well-rounded discussions on the particular challenges of using gene therapy for the diseases in question. In particular, the final chapter on lung transplantation provides an excellent discussion on the challenges and opportunities of gene therapy for transplantation.

In summary, this is a book written by scientists for scientists. To date not a single person has had a lung disease cured by gene therapy, and that possibility is still several years in the future. Thus, this monograph will not affect clinical practice. However, the story of gene therapy is fascinating and can provide insight into the challenges of medical discovery. Unfortunately, the storytelling in this monograph is not its strength, and this tome's place is as a reference manual for MD and PhD gene therapy scientists.

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