

## Lung and Heart-Lung Transplantation.

Joseph P Lynch III and David J Ross, editors. *Lung Biology in Health and Disease*, volume 217, Claude Lenfant, executive editor. Boca Raton: Informa/Taylor & Francis. 2006. Hard cover, illustrated, 947 pages, \$199.95.

Twenty-six and twenty-four years have passed since the first successful human heart-lung transplantation and the first successful human lung transplantation. Since then over 2,500 heart-lung transplant and 22,000 lung transplant procedures have been performed worldwide. Lung and heart-lung transplantation have become established therapies for patients with advanced lung disease. The annual volume of lung transplant procedures has continued to increase, with a total of 1,406 lung transplant procedures and 35 heart-lung transplant procedures performed in the United States in 2005, reported by the United Network for Organ Sharing. The expanding population of post-transplant patients and the increasing national and international availability of lung and heart-lung transplantation for patients with advanced disease support the need for education about these procedures. Volume 217 of the *Lung Biology in Health and Disease* series, **Lung and Heart-Lung Transplantation**, is a comprehensive text that covers virtually all aspects of lung and heart-lung transplantation. The broad spectrum of topics covered, and the juxtaposition of historic and current clinical management review with discussion of basic science and immunology support this text's relevance and value as resource for all individuals involved in lung or heart-lung transplantation. Transplant physicians, nurses, medical personnel, and basic scientists will find this text informative.

This book has 37 chapters, by an international panel of 75 contributing authors. Individual chapters include an overview introduction and are organized into subsections that facilitate easy access to specific information. The chapters are grouped into 10 parts, which focus on specific clinical aspects of lung and heart-lung transplantation. Part I provides an overview of lung

and heart-lung transplantation, and focuses on the history and current outcomes.

Part II details transplant immunology. These essential basic-science-oriented chapters provide an understanding of the mechanisms and problems underlying allograft rejection and tolerance.

Part III consists of 8 chapters on disease-specific aspects of transplantation, including disease management, referral criteria, and post-transplant management concerns and complications. There are chapters on chronic obstructive pulmonary disease, cystic fibrosis, pulmonary arterial hypertension, interstitial lung disease, Langerhans cell histiocytosis, lymphangiomyomatosis, pediatric transplantation, living lobar transplantation, and heart-lung transplantation. There is substantial variation in the depth of material covered in this section. The chapters on chronic obstructive pulmonary disease, interstitial lung disorders, Langerhans cell histiocytosis, and lymphangiomyomatosis provide in-depth reviews of pre-transplant disease management and prognosis, as well as disease-specific post-transplant concerns. The other chapters in this section are less detailed.

Part IV addresses organ allocation in the United States, Europe, and Australia. The lung allocation scoring system recently adopted by the United Network for Organ Sharing is discussed, as are approaches to organ preservation and expansion of the pool of utilizable donor organs.

Part V provides an excellent overview of agents used for immunosuppression after transplantation, and discusses potential future approaches. The 3 chapters in this section review the mechanisms and toxicities of these agents and summarize the limited clinical data on the use of various agents in lung transplantation.

Part VI covers allograft complications, including primary graft dysfunction and airway complications.

Part VII consists of 7 chapters that focus on infectious complications. Viral, fungal, bacterial, and mycobacterial infections are thoroughly covered, and the discussions include relevant references to experience in nonpulmonary solid-organ transplant settings.

Parts VIII and IX address acute and chronic rejection and include discussions of pathogenesis, histology, and clinical manifestations. Clinical manifestations and management of acute rejection and obliterative bronchiolitis are discussed in close proximity to histologic and pathophysiologic correlations. The depth and completeness of discussion in these sections are noteworthy.

Part X covers long-term complications of lung transplantation and immunosuppression. The content and detail are quite variable in this section, which covers a limited spectrum of disorders. Cardiac, lipid, and atherosclerotic disorders are discussed in detail, as are lymphoproliferative disorders. Metabolic bone disease is discussed briefly. There is no discussion of renal complications, neurologic complications, gastrointestinal complications, or nonlymphoproliferative malignancy.

Tabular and graphical data summaries are clearly presented. However, the quality of the photographs is limited. Bronchoscopy, radiology, and histology are essential tools for the care of lung and heart-lung transplant patients, and the value of this book would have been enhanced by better photographs. The radiographs are compromised by poor resolution and diminutive image size throughout the text. The histologic and bronchoscopic photographs, reproduced in a similar manner, would have been of much greater value if printed in color with greater resolution. Whenever possible, the authors referenced and summarized pertinent available clinical outcomes studies. However, the paucity of randomized controlled studies in the field of lung transplantation must be noted. The text would have been improved by discussion of current limitations and future directions in outcomes research.

In summary, Lynch and Ross have done an excellent job in assembling and organizing a single text that covers the major areas of lung and heart-lung transplantation. Though some of the topics included could have been covered in greater depth, and a few other topics could have been included, the comprehensive breadth and content of this text are commendable. The material covered in **Lung and Heart-Lung Transplantation** is detailed and up to date. It provides both essential background and in-depth dis-

discussion in a clear and organized manner. This would be an excellent resource for any individual who cares for lung or heart-lung transplant recipients.

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**My Office Is Killing Me! The Sick Building Survival Guide.** Jeffrey C May. Baltimore: Johns Hopkins University Press. 2006. Soft cover, illustrated, 317 pages, \$18.95.

Air quality in the workplace has bedeviled workers and managers for decades and has cost millions of dollars in lost work time, illness, and building renovations. Building occupants have searched for information to understand the nature and source of the air quality problems, possible adverse health outcomes, and effective solutions. Jeffrey May, a master's-prepared organic chemist, adds to the current popular literature with his third book, **My Office Is Killing Me! The Sick Building Survival Guide**. This very readable, 317-page book targets the general public and office occupants, rather than an academic or health-and-safety practitioner audience.

The book has 3 parts: The Basics; Daily Life; and The Final Test: Grading the Air. A brief resource guide, chapter-specific bibliography, and useful index complete the text. Each chapter includes a highlighted section of "Practical Steps," which summarizes the chapter and emphasizes specific activities the building occupant can do today to reduce or eliminate potential exposures. Scattered throughout the text are black-and-white pictures of mold and problem buildings, presumably investigated by May. Also included are 14 color plates of problematic ventilation systems and moldy buildings.

The 7 chapters in Part I give an overview of adverse health outcomes that could be related to building contaminants. This section outlines potential exposure sources, identifies projected costs of poor indoor air quality, discusses building-related construction and interior elements that could be sources of contaminants, and describes air performance and gas and particulate classes

of contaminants. May provides very accessible explanations of the fundamental gas and particulate principles and their performance in air streams, which is among the book's high points. Missing from this section is discussion of persistent bio-accumulative toxins, such as flame-retardants, which are of particular concern to women of child-bearing age.

The 5 chapters in Part II are devoted to venue-specific case studies. Though the book's title implies that the emphasis is on the traditional office environment, Section 2 has case studies of indoor air quality challenges in schools, public places, retail establishments, health care institutions, recreational facilities, and hotels. The case studies are from problems that May has problem-solved, some of which are dramatic examples of construction or building management problems. No information is provided about the total number of buildings evaluated (with and without reported air quality problems), so the reader is left to wonder if there is any venue that isn't subject to faulty construction or neglectful management. This section would have benefited from some reflection on the contribution of occupant outrage, labor/management problems, or underlying personal health problems as contributors to symptom reporting.

The final section discusses, in 3 chapters, strategies for testing air quality, including when to hire and what to expect from a professional. Though most building occupants are unlikely to ever use some of the sampling equipment described, they may be in a position to interpret the findings reported by consultants. To that end, May provides information on typical measurement results, though the range of exposures and the clinically relevant health effects related to documented exposures are not presented. There is considerable emphasis here and elsewhere in the book on mold, and May rightfully notes that there are no regulatory requirements for evaluating, measuring, or controlling mold in indoor environments. The reader would have benefited from a more in-depth discussion of the limitations of mold sampling and why regulating the office environment has eluded us.

**My Office Is Killing Me!** appears to be a modest rehash of elements of May's earlier books, with few references to recent research and other publications. His selection of chapter titles and case studies reflect his apparent bias toward problem environments—understandably, since his business

as a consulting Certified Indoor Air Quality Professional probably takes him to worst-case, rather than typical, buildings. However, less inflammatory word choices and examples would help the reader put office indoor air problems into more realistic perspective.

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**Bronchial Vascular Remodeling in Asthma and COPD.** Aili Lazaar, editor. *Lung Biology in Health and Disease*, volume 216, Claude Lenfant, executive editor. Boca Raton: Informa/Taylor & Francis. 2006. Hard cover, illustrated, 233 pages, \$199.95.

**Bronchial Vascular Remodeling in Asthma and COPD**, edited by Aili Lazaar, is volume 216 of the highly successful and authoritative *Lung Biology in Health and Disease* series (executive editor Claude Lenfant). Ten chapters, comprising 226 pages, form the contributions of 20 internationally renowned and highly respected authors from the Netherlands (3 authors), Belgium (4 authors), Australia (2 authors), Italy (2 authors), the United States (6 authors), Thailand (1 author), and the United Kingdom (2 authors). The aim of the book is to review and update the specialist pulmonary physician, pathologist, and scientist on bronchial circulation, rather than the better known pulmonary circulation. The chapters deal specifically with its intrauterine development, factors that regulate angiogenesis and vasculogenesis, its involvement in pathogenesis, especially that of asthma or chronic obstructive pulmonary disease (COPD) and, to a much lesser extent, pulmonary hypertension. These chapters lead naturally to speculation as to how such new information may impact the development of novel therapies or enhance current treatments.

The introduction by Lenfant provides one of several definitions for the widely used term "remodeling" to describe structural change.

Chapter 1 (23 pages and 131 references) focuses on developmental origins and ex-

perimental approaches to the study of bronchial vascular structure and function. In my opinion, with my bias as a pathologist, the introductory anatomy section should be required reading for the wider readership and is essential to understanding the information presented later in the book and that information's relevance to respiratory conditions. The first 2 line diagrams (in figure 1) are excellent and allow the reader to appreciate immediately the extensive nature of the bronchial supply, its source and drainage, and, importantly, its unique spatial and functional relationship to the pulmonary circulation and airway wall and its lumen.

The angiogenic process that occurs during normal lung development is then described. It is reasonably well illustrated, albeit the quality (contrast) of some of the illustrations is disappointing. The processes of angiogenesis (the branching of new vessels from existing ones) and vasculogenesis (emergence of entirely new vessels from "blood lakes") are distinguished. The results of studies of these processes in experimental animals, as their lungs and the air-blood barrier develop, are described. Examination of serial histological sections of a carefully selected human series demonstrates the features characteristic of the processes in humans.

The influence of genetic/local environmental interactions are described briefly. There are specific examples backed by evidence of the effects of gene deletion, using examples of the effects in gene knockout mice: vascular endothelial growth factor (VEGF), its receptor, and angiopoietin-1 emerge as key molecules, not only in the developing lung but also in the adult. Structure and function are considered in health, as are humoral and neural control. The chapter ends by considering the alterations that may occur in asthma, during allergic responses, in chronic bronchitis, in response to infection, and in emphysema. Many of the references are classic; some newer references would have added a sense of freshness.

Chapter 2 (19 pages and 105 references) deals concisely with the noninvasive measurement of airway blood flow. It begins by discriminating flow to the "submucosa" or "airway blood flow" and "bronchial (total) blood flow"; the latter includes the outer bronchial wall. It then goes on to state that "the major portion of bronchial blood flow is distributed to the mucosa (airway blood flow)." I know that the authors do not in-

tend confusion here, but those statements do not scan well, and the confusion is compounded by different applications in the text of the microanatomic terms "mucosa," "subepithelial," and "submucosa."

The fundamental section on the structural and functional basis of noninvasive measurement technique is clearly written and will be particularly helpful to basic researchers and nurses. The illustration of component histological parts is excellent, but, as the authors highlight in the text, these structures differ substantially between species and vary within humans, so the legend should have stated the species (non-human?). The functional consequences of the microanatomic arrangement are concisely and clearly described and beautifully illustrated in a line diagram (Figure 2).

The roles of the bronchial circulation in nourishment, air conditioning, and airway gas exchange are discussed/debated. The development of measurement techniques is presented with a historical perspective, and there are clear explanations of the laser Doppler velocimetry and soluble gas uptake methods. After theoretical considerations are discussed, the soluble gas uptake technique, which is the only one proven accurate and suitable for measurements in humans, is described in detail, including practical aspects, which will be valuable to those who plan to have hands-on experience. Data are presented from human subjects and asthmatics, obtained from experiments on the effects on airway blood flow of vasoactive substances and of usual asthma medications. The references span much time, but few of them are recent.

Chapter 3 presents the molecular mechanisms of angiogenesis in 35 pages, with extensive (261) and relatively recent references. It is a meaty chapter, not for the faint-hearted, but highly interesting, especially to the biologist, pulmonary basic researcher, and clinical scientist. The chapter begins by suggesting the relative molecular links that have been proposed between angiogenesis and pathogenesis and the progression of chronic disease, which reminds the reader that this is as yet only an emerging field. It subdivides the processes of vessel growth by defining terms such "vasculogenesis," "angiogenesis," "arteriogenesis," and "collateral growth."

The central role of VEGF and interaction with its several tyrosine kinase receptors is explained in detail before considering important influencing molecules such as pla-

cental growth factor. The role(s) of other putative angiogenic factors at different stages of vascular development and in response to various stresses, including those that occur in pulmonary disease, are then considered. Vasculogenesis genes and molecules considered include CD31, CD34, transcription factor Tal-1, the polymorphic immunodominant molecule (PIM-1), the erythroblastosis virus E26 oncogene (Ets-1), Hex, vascular endothelial zinc finger-1 (VEZF), Hox, Id-1, Tie-1, Tie-2, vascular endothelial cadherin, cloche, basic fibroblast growth factor (bFGF), members of the GATA family, and influences by endothelial growth factor (EGF), platelet-derived growth factor (PDGF), and transforming growth factor  $\beta$  (TGF- $\beta$ ), which are molecules already associated with airway diseases.

The existence of an endogenous source of angiogenic progenitors has generated excitement about possible therapies. Molecules involved in angiogenesis include matrix metallo-proteases, VEGF, platelet/endothelial cell adhesion molecule (PECAM-1) and vascular endothelial cadherin, angiopoietin-1, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), insulin-like growth factor (IGF-1), and thrombospondin (TSP-1). In the lung, signaling via the morphogen, sonic hedgehog, and Gli proteins is critical . . . and the interesting list goes on. A table or diagram of all these molecules and the stages of their main involvement in vascular development or response to injury would have been of assistance to the more general reader. These molecules could have been tabulated in relation to the subheadings presented: angiogenic progenitors in vasculogenesis, early stages of angiogenesis, endothelial cell proliferation, migration and vessel sprouting, vascular tube formation, assembly of the vascular network, long-term survival of the endothelium, endothelial diversity, periendothelial cells, and collateral vessels. The review provides a very interesting, detailed, and worthwhile glimpse into the field of vascular research.

Chapter 4 (23 pages and 115 references) focuses on the influence of chemokines on angiogenesis. These are small (8–12 kilodaltons) peptides, and the 40 or so currently identified are shown classified into 4 supergene families in Table 1 in Chapter 4. Though we instinctively think of these molecules in the recruitment of inflammatory cells, the authors explain the importance of the "ELR" (glutamic acid, leucine, arginine)

sequence motif in endothelial cell chemotaxis and neovascularization. Chemokine receptors and binding is then explained, as is receptor identification and their localization to endothelial cells. Pro-angiogenic and anti-angiogenic interactions are given as examples. This is followed by consideration of several signaling pathways, then by interesting, albeit mainly speculative, discussion of the potential role of chemokines in angiogenesis in the lung, in asthma and COPD, and in pulmonary artery obstruction, lung neoplasia, and bronchopulmonary dysplasia.

Chapter 5 (20 pages and 139 recent references) deals with the critical influence of the extracellular matrix on vascular homeostasis in pre-existing vessels and its role in the endothelial response to injury or pathology. It begins by describing the normally low turnover of endothelial cells and the main extracellular-matrix constituents and growth factors that lie adjacent: thrombospondins, high-molecular-weight hyaluronan, collagen VIII, endostatin, pigment epithelium-derived factor, VEGF, and bFGF. On initiation of angiogenesis, the process of matrix transformation is described; its onset is associated with increased vascular permeability, release of adhesive proteins, de novo protein synthesis, and secretion of pro-angiogenic and inhibitory molecules such as perlecan and SPARC (secreted protein, acidic and rich in cysteine), respectively.

Proteolytic processing of the extracellular matrix is then described, followed by sections considering interactions between the extracellular matrix and integrins, and the processes of endothelial cell proliferation, apoptosis, migration, and capillary morphogenesis (ie, the formation of tubular networks).

Chapters 6, 7, and 8 reflect the title and primary focus of the book: vascular remodeling is considered in asthma, chronic bronchitis/emphysema, and COPD, respectively. In Chapter 6 (19 pages and 183 references), the observed changes to airway wall vessels in asthma of varying severity are described. The authors explain the controversies and the differences in vessel measurement methods. They report on the localization and role of VEGF and how wall thickness may arise due to an increase in vessel number, vasodilation, or leakage. In Tables 1 and 2 they list angiogenic and anti-angiogenic factors of potential relevance to airway disease, and in Tables 3 and 4 they list factors known to

regulate leakage and vasodilation, respectively. Finally, there is reasoned speculation as to the potential role of bone-marrow-derived stem cells and the factors that might mobilize such CD34+ cells.

In Chapter 7 (21 pages and 108 references) the pathologies of emphysema and chronic bronchitis are briefly reviewed. The chapter describes the role of reduction of blood supply to alveolar precapillary blood vessels in the pathogenesis of emphysema (ie, the original vascular atrophy model proposed much earlier by Leibow). Vascular remodeling in COPD is then considered, with the focus on the *pulmonary* rather than bronchial circulation and on hypoxia-driven vasoconstriction. The flow between these sections is poor, and there is repetition. A section reiterates the general processes involved with angiogenesis, without particular reference to COPD. In the section on "bronchial vessels" there is a switch back to the authors' own findings about *pulmonary* vessels, which is confusing. The section on growth factors is repetitive of what was dealt with earlier in the book, albeit they do present their own data showing increased expression of VEGF in the airway epithelium, airway smooth muscle, and vascular smooth muscle in patients with COPD. The meat of the chapter is in Section V, where the results of examination for angiogenic growth factors in COPD are provided and summarized nicely in Table 2. It is clear from this and the following section that there is much to be done.

In contrast, Chapter 8 (27 pages and 129 references) focuses entirely, and in clear fashion, on *pulmonary* vascular remodeling and pulmonary hypertension in COPD, rendering obsolete much of what was said on this subject in the previous chapter. Pulmonary vasculature and its development are clearly set out and complement the information on *bronchial* vasculature in Chapter 1. Pulmonary capillary pressure/flow relationships are explained. The effects of COPD on pulmonary hemodynamics and vasculature are presented. The accompanying morphological changes are described in muscular and then nonmuscular arteries. Then there are 2 sections on the cellular changes and mechanisms that probably contribute to these changes. Specific examples of growth factors and vasoactive mediators are given with relevant data on patients with COPD, along with interesting, well reasoned speculation. Even before COPD is detected, cigarette smoke can be associated (in both

human and animal studies) with vascular changes, and these interesting findings are presented. The chapter ends with sections on genetic influences and a consideration of possible therapeutic approaches. This is an excellent, interesting, and well-structured read.

Chapter 9 (15 pages and 93 references) presents a short review of the lessons learned from studies of skeletal muscle, especially exercise-induced angiogenesis. It begins, however, by considering what is known about cancer and stresses the importance of hypoxia as a stimulus. It reiterates what are considered the key pro-angiogenic factors generally, and then focuses on skeletal muscle in Section III and beyond. Genes activated by exercise (and hypoxia or nitric oxide) are given and experimental animal data are cited. The chapter ends with comparisons of their findings with what is known about the pulmonary system and focuses on VEGF as a key molecule.

Chapter 10 (13 pages and 71 references) summarizes what is known about current therapies and novel approaches in the pharmacologic modulation of bronchial vascular remodeling. The reductive effects of corticosteroids are given by example of the authors' own data, and a number of potential mechanisms for a steroid effect are presented, which demonstrate its complexity of action. Effects of  $\beta_2$  agonists and their potential to interact with steroids are explained and summarized in a table. The effects of leukotriene antagonists on blood flow are given, and apparently nothing is known of the effects of theophyllines in this regard. The chapter ends with consideration of novel approaches and drug targets, including the anti-leakage effects of angiotensin-converting enzyme inhibitors. Endogenous inducers and inhibitors of angiogenesis are usefully summarized in table form.

I would recommend this book to pulmonary specialists, particularly those active in research.

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**Malignant Pleural Mesothelioma.** Kenneth O'Byrne and Valerie Rusch, editors. Oxford: Oxford University Press. 2007. Hard cover, illustrated, 646 pages, \$198.50.

With the increasing incidence of diffuse malignant mesothelioma on a global basis, there have appeared monographs in the past few years devoted solely to this tumor, and this book is one of the best. The editors selected 59 authors from around the world, in a truly global approach to the problem, and from multiple disciplines, including epidemiology, molecular medicine, pathology, radiology, surgery, and oncology.

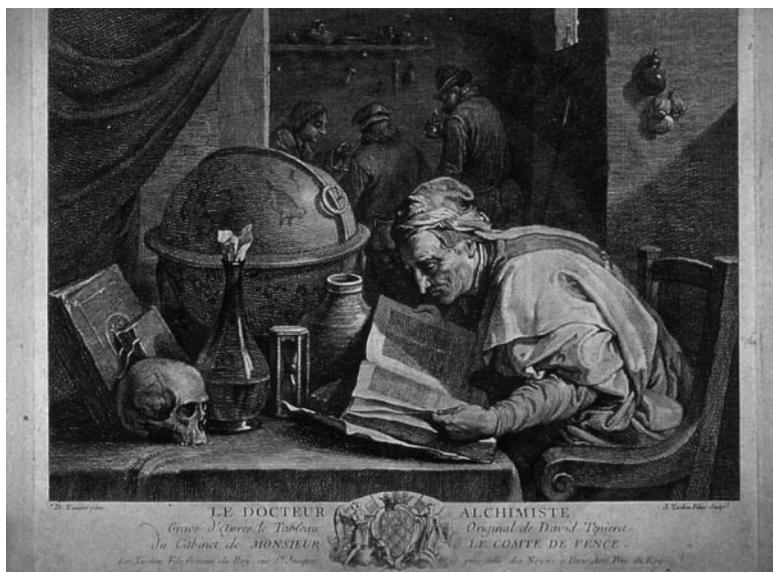
The book will appeal to anyone concerned with this asbestos-related disease, and it includes new information, particularly about the geographical distribution of the disease, molecular mechanisms of the disease, clinical staging, and the most current roles for chemotherapies and surgeries. In a book with many authors, there is almost inevitably some overlap in coverage, but it would be difficult to find more lucid summaries of some of these topics, including the role of vascularization and immunobiology in this tumor. The writing is for the most part clear and in a style that will be understandable across disciplines.

Anybody dealing with diffuse malignant mesothelioma, in either a research or clinical

setting, should learn a great deal from this book in topics outside his or her own immediate specializations. As this clinically relentless disease continues to increase but has proven so refractory to therapy, any additional knowledge is welcome indeed, and this book is also welcome indeed.

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Le Docteur Alchimiste  
 Engraving by J Fillius Tardieu  
 after a painting by David Teniers, 1736?  
 Courtesy, National Library of Medicine