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Orphan Lung Diseases

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T. Welte

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This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems needed to investigate it. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this Monograph.

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Guest Editor

J-F. Cordier

J-F. Cordier is Professor of Respiratory Medicine at the Claude Bernard University and Head of the Department of Respiratory Medicine at Louis Pradel Heart and Lung Hospital in Lyon, France. He is also Head of the national Reference Center for Rare Pulmonary Diseases and the Rhône-Alpes Regional Competence Center for Pulmonary Hypertension.

He served as the Head of the European Respiratory Society (ERS) Clinical Assembly and as President of the Société de Pneumologie de Langue Française.

J-F. Cordier has been involved in the field of rare ''orphan'' diseases for many years. In 1997, he wrote an editorial which was published in the journal *Le Monde*, entitled ''Orphan diseases: the silent exclusion''.

He participated in the preparation of the French National Plan for Rare Diseases (2008–2010), as well as the second National Plan (2011–2014), and has been involved in both committees at the French Ministry of Health. In 1993, he founded the Groupe d'Etudes et de Recherche sur les Maladies ''Orphelines'' Pulmonaires (GERM"O"P), a collaborative group of French clinical researchers investigating rare pulmonary diseases. GERM"O"P has published a number of articles on eosinophilic pneumonias, hereditary haemorrhagic telangiectasia, microscopic polyangiitis and lymphangioleiomyomatosis. He has also contributed to the description of cryptogenic organising pneumonia, pulmonary amyloidosis, idiopathic nonspecific interstitial pneumonia, and the syndrome of combined pulmonary fibrosis and emphysema. Together with S.R. Johnson he published the ERS guidelines for the diagnosis and management of lymphangioleiomyomatosis.

He has been involved in the following consensus statements as a co-author: American Thoracic Society (ATS)/ERS idiopathic pulmonary fibrosis diagnosis and treatment: international consensus statement in 2000; ATS/ERS Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias in 2002; and the ATS/ERS/Japanese Respiratory Society (JRS)/ Asociación Latínoamericana de Tórax (ALAT) statement on idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management in 2011.

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Preface

Rare lung diseases are one of the most exciting topics in respiratory medicine. However, as these are infrequent diseases evidence-based guidelines do not exist for most of the different entities. Nevertheless, progress has been made during the last decade either in diagnostics or therapy, which has greatly changed clinical practice. This issue of the *European Respiratory Monograph*, with contributions from well-known experts in the field, summarises the current knowledge of orphan lung disease in one edition for the first time. This allows respiratory physicians, either in the clinic or in research, to obtain an overview about the whole field of these diseases.

I would like to congratulate the Guest Editor, J-F. Cordier, for all his hard work in putting together this excellent Monograph, which will be of interest to medical doctors, in general, and especially respiratory physicians. I am convinced that they will find this Monograph useful in their daily practice.

Editor in Chief
T. Welte

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Introduction

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Chest physicians may sometimes feel that they are not directly concerned by rare or so-called orphan lung diseases, supposing such diseases are reserved for specialists working in university centres. However, this is not true as patients with such diseases are distributed throughout the country, and can begin their diagnostic trajectory close to the place where they live. Thus, any chest physician will meet several patients with rare diseases during his career.

The term ''orphan'' disease means that affected patients feel that almost nobody cares about their disease and that none or little research is performed to improve diagnosis, clinical management, and to elaborate or commercialise drugs to treat the condition. The patient, therefore, feels abandoned and as such like an ''orphan''. Orphan diseases may commonly be neglected but can be frequent diseases in low-income countries, especially tropical diseases, such as trypanosomiasis. As the population of such countries does not have the money to buy drugs, many pharmaceutical companies are reluctant to invest in research for these non-solvent populations. In most developed countries orphan diseases are largely rare diseases that are little known to the public and even to doctors.

A disease is defined as rare in Europe if it affects less than one in 2,000 persons. However, this definition covers a strong disparity, as some disorders affect several thousand or tens of thousands of patients, whereas others affect only a few hundred or even a few dozen patients throughout Europe. Approximately 8,000 different rare diseases have been identified, 80% of which are considered to be of genetic origin. If most of the rare genetic diseases are present at birth or during childhood, others may manifest only at adulthood. Furthermore, the clinical phenotypes of the rare diseases may be varied, thereby complicating diagnosis and care, particularly when several organs are involved.

Patients with rare disease feel orphaned in the healthcare world and a lack of solicitude. They are often disappointed and angry by failure to diagnose or misdiagnosis, which can occur for months or even years before they eventually find an experienced clinician. Diagnosis is especially difficult when the disease imitates a more common disorder. Furthermore, as teaching in medical schools cannot cover the many rare diseases it is unavoidable that general practitioners do not know all of the estimated 8,000 rare diseases. Therefore, the specialist must have the capacity to suspect the diagnosis in their own field and further orientate the patient towards expert centres, where the final diagnosis may be confirmed and the management defined, if necessary.

The orphan lung diseases or orphan diseases including lung involvement have not yet been precisely indexed. Some of these are of genetic origin (*e.g.* hereditary haemorrhagic telangiectasia), others are acquired, systemic diseases that comprise pulmonary involvement (*e.g.* vasculitis), whilst others only concern one sex (*e.g.* sporadic lymphangioleiomyomatosis, which affects only females). Some orphan diseases have become just rare diseases because dedicated research has resulted in efficient drug discovery and commercialisation (*e.g.* idiopathic pulmonary arterial hypertension).

The interest of chest physicians for rare/orphan diseases has increased, over recent years, for several reasons. These include, amongst others, the advancement of diagnostic tools *e.g.*

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high-resolution computed tomography (HRCT), which can be used to identify characteristic diagnostic patterns (*e.g.* the crazy paving pattern of alveolar lipoproteinosis on a chest HRCT). Furthermore, patients may ask for more relevant investigations as they themselves glean precise medical information, regarding their condition, from the internet. Chest physicians should, therefore, know where they can obtain credible and updated information to launch the appropriate investigations and attain a correct and final diagnosis for their patients. The information may be obtained directly from original papers, published in specialty journals; however, these are often focused on basic research that has limited immediate application. Thus monographs, such as the present one, may represent a true companion for reaching a secure diagnosis in the jungle of orphan lung diseases.

The US Orphan Drug Act made law in 1983 has provided incentives to the pharmaceutical industry to improve rare disease drug development. In Europe the regulation of the European Parliament and of the Council on Orphan medical products was adopted in 1999. This has resulted in an increasing number of ''orphan drugs'' being approved for clinical use in recent years.

Associations for patients with rare diseases continue to play a specific role in supporting patients dealing with daily difficulties, distress and isolation. They help in translating the medical information concerning the disease and the patients care into common, understandable laymen's language, often bringing responses to practical questions that many patients may not ask the doctor. The more powerful patient associations further fund medical research projects and meetings. They must collaborate with, but remain independent from the medical specialists of the disease to best play their role. Their input is needed in all the networks, referral centres, and clinical research projects. The sizes of the associations are extremely variable, largely dependent on the prevalence of the disease. Patient associations are usually nation based, especially for linguistic reasons. Some federations of patients' associations exist on a European basis. These associations further participate in the European Organisation for Rare Diseases (EURORDIS), a non-governmental patient-driven alliance of patient organisations and individuals that are active in the field of rare diseases and dedicated to improving the quality of life of all people living with rare diseases in Europe.

The European Union Committee of Experts on Rare Diseases (EUCERD) recently produced recommendations on the quality of criteria for national centres of expertise concerning rare diseases. The experts emphasised the need for the expertise to travel rather than the patients themselves to travel. Cooperation and knowledge sharing between centres of expertise appears to be an efficient approach to dealing with rare diseases in Europe. EUCERD recommended the identification of appropriate centres of expertise throughout their national territory, thereby fostering the participation of these centres in a European reference network, to organise healthcare pathways for patients and to support the use of information and communication technologies, such as telemedicine, where necessary to ensure distant access to specific healthcare.

For too long orphan diseases have been a matter of curiosity to the public and to doctors, rather than an obligation of solicitude to the affected patients. The time has come to develop efficient care, especially through more appropriate diagnosis and research, including drug development and a more humanistic consideration of the patients who should no longer be made to feel like an ''orphan''.