Introduction

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Asthma has been recognised since early civilisation and has been well described by physicians over the centuries, with particular understanding of mechanisms from physicians in the 19th and 20th centuries [1]. For example, at the turn of the 20th century, William Osler (1849–1919) indicated in the "*Principles and Practice of Medicine*" that asthma was caused by muscular contraction, mucosal oedema and the presence of mucus in the lumen of the airways, laying the foundation of our current understanding of the nature of asthma [2]. However, real therapeutic breakthroughs only began to emerge in the latter part of the last century with the discovery of the bronchodilator effects of adrenaline and the anti-inflammatory effects of injected cortisone in the 1950s [3]. It then took nearly 20 years to demonstrate the efficacy of inhaled corticosteroids in chronic asthma [4], and a further 20 years for their use to be combined with long-acting β_2-adrenergic agonists making this one of the most effective treatments available for symptomatic asthma [5].

In parallel with the development in the modern treatment for asthma, there was growing concern for the increase in asthma prevalence and its severity, particularly in Western industrialised countries. Various surveys undertaken amongst asthmatics indicated a picture of continuing morbidity with increasing asthma fatalities. This led to the initiation of national guidelines for the management of asthma starting in Australia and Canada, shortly followed by several other countries and culminating in the Global Initiative for Asthma (GINA) guidelines [6]. It is likely that these guidelines have been instrumental in the reduction of death rates observed in several countries. In Finland a concerted governmental action against asthma has led to a significant reduction in morbidity and costs concerning asthma, as well as the impact on individual asthmatics and on society in general [7].

It appears that the battle for control of asthma is being won. However, amongst these improvements in asthma treatment and management approaches, which have certainly been beneficial to many asthmatics, physicians have always encountered difficult-to-treat asthma patients in their practice and these are emerging as one of the remaining challenges in asthma. This group constitutes only one in every 10 or 20 asthmatic patient and can be labelled as "difficult-to-treat severe asthma". Another term is "therapy-resistant asthma", which is very apt since these patients do not show significant beneficial responses to current therapies. The management challenge for the physician is to determine whether these patients are indeed asthmatics and whether they are receiving and taking the most appropriate treatments for their disease. Such patients often undergo different combinations and iterations of available treatments, sometimes at high doses and often suffering from the costly consequences of long-term systemic corticosteroid use, yet they continue to suffer from uncontrolled asthma.

A decade ago another milestone in asthma was set with the recognition of this problem of severe asthma by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) with the publication of definition statements of "difficult-to-treat asthma" and on the way forward [8, 9]. The acceptance of a common definition has focused on the clinical description and phenotype of the

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severe asthma patient. To make the definition more widely applicable, a global definition was recently published under a World Health Organization (WHO) consultation on severe asthma [10].

It is quite clear that the questions that needed to be answered in the 1990s were as follows. 1) What does the patient with severe asthma look like? 2) Why have these patients developed severe asthma? 3) How should existing treatments be used and what new treatments can be given to control severe asthma? 10 years on and these questions are still unanswered; however, there are now important insights from the information that has been obtained from research into severe asthma during this time. Perhaps the most pertinent information is how the disease is heterogeneous, and the challenge for the next 10 years would be to understand the different types of severe asthma.

It is also important to determine whether severe asthma represents an altogether different new form of asthma. If one espouses the generally accepted notion that asthma is the result of a complex gene–environment interaction then it could make sense. Certainly, the world has changed more rapidly over the past 25 years than it has in the previous 100 years, in terms of both the environment lived in and lifestyles. It is quite pertinent to ask whether environmental changes could have led to the increase in asthma prevalence and increasing severity of asthma, perhaps through epigenetic changes. Is it a result of disordered immunity to the new challenging environment of allergens, pollutants and infections? Would this drive the inflammatory response that leads to severe asthma? It is important that such questions and other related issues be asked and be answered.

The Guest Editors of this Monograph are fortunate to be part of an ongoing ATS/ERS Task Force on severe asthma, through which an eminent group of experts were asked to contribute to the Monograph. The task asked of them was to describe what we have learnt, what are the objectives for the next 10 years, and what milestones can be expected at the end of the next decade. We would like to thank all those who have contributed and we greatly appreciate the time and commitment they spent on this project. We would also like to thank the ERS Publications Office for their enthusiasm and hard work.

The burden of severe asthma is substantial and expectations for better treatments are high. We hope this Monograph represents a small step towards achieving these goals.

Statement of interest

K.F. Chung has been reimbursed for travel expenses to international meetings and received honoraria for speaking at meetings sponsored by GlaxoSmithKline, AstraZeneca and Novartis. K.F. Chung has participated in advisory boards meetings of GlaxoSmithKline, Boehringer Ingelheim and Novartis, and received unrestricted research funding from GlaxoSmithKline and Pfizer; and has taken part in clinical trials organised by GlaxoSmithKline, Novartis and Asthmatyx. E.H. Bel has received a fee for speaking from GlaxoSmithKline, has received funds for research from GlaxoSmithKline and Novartis, and has received fees for consulting from MSD and Novartis. S.E. Wenzel's institute, the University of Pittsburgh, has received money for mulitcenter research studies from MedImmune, GlaxoSmithKline, Amgen, Cephalon and Aerovance. Monies received in each case by the University of Pittsburgh were $<$100,000 US$. S.E. Wenzel received consulting funds from GlaxoSmithKline, Merck, Amira, Amgen all $<$10,000 US$.

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