Asthma: still more questions than answers

As we did in 2006, we are dedicating this week's issue to asthma to coincide with the European Respiratory Society meeting to be held in Berlin, Oct 4–8. In collaboration with the Society, *The Lancet* is hosting a hot-topic session at the conference that discusses new targets for drug development, insights into the use of inflammatory markers, new understanding of the complexity of disease progression and exacerbation, and new concepts of pathogenic mechanisms. So how much progress has been made in the understanding, treatment, and prevention of asthma? Despite intense epidemiological and basic research, three fundamental questions remain tantalisingly puzzling. What is asthma? Who gets asthma and why? Which factors predict exacerbations and treatment response?

First, what is asthma? With every new piece of the puzzle, the notion of asthma as one unifying disease concept is disappearing further into the realm of historical oversimplification. Further to the now widely accepted fact of differing clinical phenotypes, Gary Anderson shows elegantly in this week's issue that there are equally differing pathogenetic phenotypes or endotypes, as he calls them, which together with clinical phenotypes will hopefully lead to a more precise classification of distinct wheezing disorders. 2 years ago, we made a plea to abandon asthma as a disease concept. This plea is now more justified than ever. Asthma is at best a syndrome with different risk factors, different prognoses, and different responses to treatment. Without better understanding of the underlying differences, targeted treatment efforts with improved outcomes will be incomplete and prevention will remain elusive.

Second, who gets asthma and why? In addition to previous identification of distinct childhood wheezing patterns that are likely to lead to persistent asthma, Debra Stern and colleagues analyse data from one of the earliest and best characterised birth cohorts, the group with so-called new-onset adult asthma, and show childhood origins even for this group. Evidence from Phase Three of the International Study of Asthma and Allergies in Childhood points towards an association of paracetamol use in infancy and early childhood and the risk of asthma and eczema. And data from the European Community Respiratory Health Survey identify rhinitis, even if non-atopic, as a powerful risk factor for adult-onset asthma. All these findings underscore the likely importance of gene–environment interactions in prenatal life and early childhood for the development of inflammatory airway disease later in life. In their Review, Peter Sly and colleagues advocate early identification of children with atopy to enable treatment, allergen avoidance and immunotherapy, and close follow-up. Early intervention trials with long follow-up are needed to assess the feasibility of reducing asthma incidence and prevention.

The third question centres on treatment success. Treatment ideally achieves a steady state of no asthma-related symptoms and no exacerbations with minimum continuous or intermittent treatment. In practice, although this is achievable in most patients with mild asthma, many patients with more severe disease will not be optimally controlled. Treatment success varies from patient to patient, can change rapidly with exposure to environmental triggers, and depends highly on the correct use of guidelines by primary-care physicians and adherence to treatment by patients. In Stanley Szefler and colleagues' study, 77% of inner-city adolescents did not have good control of their asthma at enrolment. After the run-in period, in which all were treated according to standard guidelines, only 30% continued to have poor control.

So, much improvement can already be achieved by using, and ensuring adherence to, existing guidelines. However, guidelines are complex. A recent one, issued in 2007 by the US National Asthma Education and Prevention Program, is 440 pages long. Adherence is dependent on many factors, including the affordability of expensive inhalers. Urs Frey and Béla Suki explain in their Review how risk assessment for exacerbations needs to take the complexity of asthma into account with a multidimensional approach that includes long-term assessment of disease fluctuation. Whether busy primary-care physicians will have the time and expertise for such an approach is questionable. Perhaps the future lies in highly personalised treatment and monitoring, aided by computer-based algorithms.

Progress in understanding asthma and its underlying mechanisms is slow; treatment can be difficult and response unpredictable; and prevention or cure is still a pipedream. Asthma, one of the most important chronic diseases, remains a genuine medical mystery. ■ *The Lancet*

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