

Editorial

The causes of asthma: the need to look at the data with different eyes

Josep M. Antó

Respiratory and Environmental Health Research
Unit, Municipal Institute of Medical Research
(IMIM-IMAS), Barcelona, Spain

Josep M. Antó
Respiratory and Environmental Health Research Unit
Municipal Institute of Medical Research
(IMIM-IMAS)
Universitat Pompeu Fabra
Barcelona,
Spain

Accepted for publication 23 December 2003

In a recent film by the Coen Brothers, Joe – a professional killer suffering from asthma – kills himself when, in the middle of a big mess, he shoots his victim with his inhaler and simultaneously inhales his own bullet (1). Is the research on the origins of asthma at risk of a similar death due to the abundance of speculative theories, inconsistent findings and the difficulty in clarifying some of the fundamental issues? Perhaps.

Over the last decades we have seen an epidemic increase in research about the aetiology of asthma, paralleling its widespread increase in prevalence. Research in modern epidemiology in the 1950s was fuelled by an epidemic in lung cancer in Europe and the US (2). However, while research on lung cancer led to the now uncontroversial evidence that lung cancer is mainly caused by smoking cigarettes, this has not been the case with asthma, where nearly two decades of intense research has neither provided robust evidence nor any widely accepted answer about its origins. This issue of *Allergy* features a remarkable quartet of reviews focusing on different issues of asthma (3–6). While these four reviews provide a very valuable update on current knowledge about the determinants of asthma, they also show the lack of well established answers. Why? Causality is a concept placed at the heart of scientific knowledge. A landmark of modern medicine has been the development of logic systems for understanding causality, mainly the Koch's postulates and the Hill's criteria with their several adaptations (7). Using these interpretative systems, and based on experimental, clinical and epidemiological research, it has been possible to identify several relevant determinants of some leading causes of death like cancer,

atherosclerosis and infectious diseases. Why, however, has the type of research that has been reasonably successful in other diseases been less so in asthma? Probably because we have been facing at least three, so far, insoluble difficulties: (i) sorting out the risk factors of incidence from those of prevalence, (ii) understanding its complex time course, and (iii) developing a sufficiently valid and operative definition of the disease.

The difficulty of distinguishing between the risk factors of incidence and those of prevalence can be fully appreciated by a careful reading of an article about the causal relationship between exposure to house dust mites and asthma in which the authors review the Hill's criteria of causality against the available evidence (8). Although the authors conclude that there is convincing evidence that all the relevant criteria are met, strongly supporting the theory that exposure to house dust mites is a cause of asthma, their analysis has the fundamental flaw of ambiguously mixing incidence and prevalence, and interpreting the results of experimental studies on sensitized asthmatics as evidence supporting the theory that exposure to mites is a causal factor of asthma. Because these studies were performed on asthmatics, they can only tell us about the evolution of the disease, not about its origin. Contrary to this conclusion, recent reports from prospective studies on newborn cohorts in Germany and the USA have shown that exposure to house dust mite allergens at birth and during the first months of life was not related to the occurrence of wheezing as a surrogate of asthma (9, 10), a counterintuitive finding considering that exposure to mite allergens was associated with sensitization and that sensitisation to house dust mites

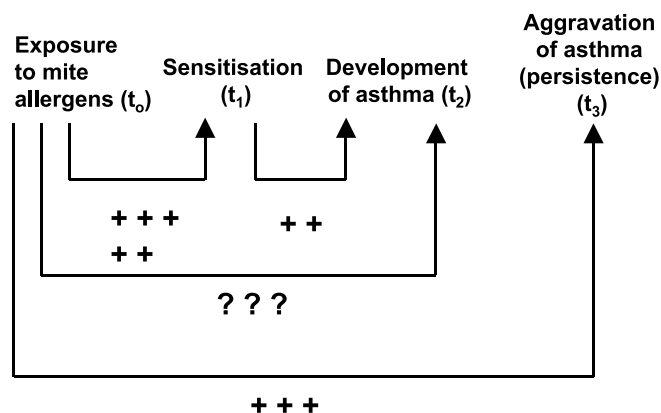


Figure 1. The lost link in the aetiology of asthma

was associated with wheezing. It should probably be a lost link in this relationship (Fig. 1), although no formal assessment has been published where such a link might include, among other possibilities, the presence of negative confounding, reverse causation, dose-response patterns and gene-environment interactions. The review by Bousquet et al. (3) on the potential importance of epigenetic mechanisms for the development of asthma shows how complex gene-environment interaction may be, and the importance of integrating the exponentially growing information on genomics with the epidemiological and clinical approach for the understanding of asthma. As the epigenetic mechanisms invoked in this review may play a role '*in utero*', it highlights the importance of understanding gene-environment interactions even before birth, a notion very familiar to most epidemiologists after Barker (11).

The epidemiological theory states that aetiology refers to environmental exposures that are previous to (time order) and conducive to (directionality) disease (incidence) and, consequently, large efforts have been devoted to identifying the risk factors of incidence in studies where exposures are first assessed in non-disease subjects who are then followed up appropriately. This approach has been notably successful in chronic diseases like coronary heart disease and cancer. Why not in asthma? It has been shown by different studies that asthma exhibits a complex time course where the intermittence of symptomatic periods is the more common pattern (12), with wheezing the predominant symptom occurring most frequently in a large proportion of children in the first months and years of life (13). Even assuming that wheezing is a valid surrogate for asthma, this time pattern may have two important consequences. First, it narrows the window of opportunity for assessing the time order between the exposure to allergens and other environmental factors and the occurrence of asthma. Secondly, it precludes the assumption that those with no asthma at a given time did not have asthma previously, a condition that is likely to go unreported if retrospectively assessed. With such a

pattern even the traditional belief that occupational asthma is the best model of incident asthma in adults is questionable. For this type of complex time pattern, epidemiology probably lacks the tools, and even the concepts, as shown by the confusing branch of causality-related terms provided either by the Last dictionary (predisposing, facilitating, precipitating and reinforcing factors) (14) or by GINA (predisposing, causing, contributing, exacerbating) (15). Instead of using ill-defined concepts, what we need is to isolate the risk factors that influence incidence from those that account for prevalence, and among the latter isolate those that are related to duration, relapse and remission. The extent to which this can be done with the available concepts and methods remains to be seen.

Last but not least, we lack a sufficiently valid and workable definition of asthma. Defining asthma has been a contentious issue for decades and still is, and although in some instances the medical sciences have bypassed the intricacies of causality by defining the disease according to its causal agents this is unlikely to be possible for asthma. As a substantial proportion of asthma is likely to begin during childhood, asthma epidemiology has increasingly focused on the first years of life and most studies have relied on wheezing as a surrogate of asthma. Because the use of wheezing involves a large degree of misclassification of asthma, sorting out its phenotypic heterogeneity is a major challenge. Some advances in understanding the cellular mechanisms of lung diseases are taking place and the possibility that these advances may result in a redefinition of asthma is a reasonable hope.

Should these important obstacles be a reason for pessimism about understanding the origins of asthma? Yes and no. Asthma prevalence is the important concept for the disease burden and it is much more accessible to investigation than asthma incidence. Understanding the environmental and genetic determinants of prevalent asthma is likely to reveal a lot about the reasons why asthma (whatever its initial causes) persists or recurs. Indeed our knowledge about the risk factors of asthma prevalence has been growing constantly over the last decades. Unfortunately, for preventive purposes, separating the initial causes amenable to primary prevention from the ones that are targeted by secondary or tertiary prevention remains important. In the paper by Gore and Custovic in this issue of *Allergy*, a thorough review of preventive trials for asthma and allergies is provided (4). Notably, results from the Isle of Wight trial, together with preliminary results from the MASS study, may be seen as evidence supporting a causal relationship between exposure to inhaled allergens and the development of asthma. Recent evidence from a cohort study also showed that exposure to cockroach allergens is a risk factor of incident wheezing in young children (10). Both ongoing prospective studies on birth cohorts, as well as primary prevention trials, are hoped to provide new and robust evidence about the causes of the development of asthma.

Widespread excitement to clarify the recent epidemic increase and the geographic patterns of allergy and asthma will remain and will stimulate new hypotheses. A new one is proposed in the present issue by Wjst, suggesting that either the increased survivability of children with a Th1 maturation defect or the lack of a Th1 environmental trigger may play a role in the increased trends of allergy and asthma (5). The comprehensive review by von Hertzen and Haatela (6) in this issue of *Allergy* illustrates how many potentially relevant hypotheses about the determinants of asthma are being investigated. Their notion that something is lacking from our affluent societies that has the capacity to protect against the development of atopic (and

autoimmune) diseases is like a paradox of the current immoral worldwide distribution of health and wealth. Without doubt, new hypotheses are always welcome, especially if they are testable. However, after two decades of intensive research about the origins of asthma without well established answers it is perhaps time to take a breath and look at the available data with different eyes. Otherwise, by fitting more and more data into our narrow frameworks we will mirror the Marx Brothers in their 'One Night in the Opera', where more and more people were crowded into the small cabin (16). Nonetheless, there is a popular relationship between brothers and atopy although the cause of such a relationship remains, again, to be understood (17).

References

1. COEN J. Intolerable Cruelty. USA: Universal Pictures and Imagine Entertainment, 2003.
2. DOLL R, HILL AB. A study of the aetiology of carcinoma of the lung. *Br Med J* 1952;**2**:1271–1286.
3. BOUSQUET J, JACOT W, YSEEL H, VIGNOLA AM, HUMBERT M. Epigenetic inheritance of fetal genes in allergic asthma. *Allergy* 2004;**59**:138–147.
4. GORE C, CUSTOVIC A. Can we prevent allergy? *Allergy* 2004;**59**:151–161.
5. WJST M. Is the increase in allergic asthma associated with an inborn Th1 maturation or with an environmental Th1 trigger defect? *Allergy* 2004;**59**:148–150.
6. VON HERTZEN LC, HAAHTELA T. Asthma and atopy – the price of affluence? *Allergy* 2004;**59**:124–137.
7. SÜSSE M. What is a cause and how do we know one? *Am J Epidemiol* 1991;**133**:635–648.
8. SPORIK R, CHAPMAN MD, PLATTS-MILLS TAE. House dust mite exposure as cause of asthma. *Clin Exp Allergy* 1992;**22**:897–906.
9. LAU S, ILLI S, SOMMERFELD C, NIGGEMANN B, BERGMANN R, VON MUTIUS E, WAHN U. Exposure to house dust mite and cat allergens and the development of asthma: a cohort study. *Lancet* 2000;**356**:1392–1397.
10. LITONJUA AA, MILTON DK, CELEDON JC, RYAN L, WEISS ST, GOLD DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. *J Allergy Clin Immunol* 2002;**110**:736–742.
11. BARKER DJ. Rise and fall of western disease. *Nature* 1989;**338**:371–372.
12. STRACHAN DP et al. The evolution of wheezing from childhood to adulthood. *Br Med J* 1996;**312**:1195–1199.
13. MARTINEZ FD, WRIGHT AL, TAUSSIG LM, HOLBERG CJ, HALONEN M, MORGAN WL. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Eng J Med* 1995;**332**:133–138.
14. LAST LM. A Dictionary of Epidemiology. Oxford University Press, 1988.
15. National Institutes of Health. Global Initiative for Asthma. USA: National Institutes of Health, 1995.
16. WOOD S and National Institutes of Health. Marx Brothers. A Night in the Opera. USA: 1935
17. SUNYER J, ANTO JM, HARRIS J, TORRENT M, VALL O, CULLINAN P, NEWMAN-TAYLOR A. AMICS study. Asthma multi-centre infants cohort study. Maternal asthma and parity. *Clin Exp Allergy* 2001;**31**:1335–1337.