EDITORIAL

Basic Research Into Asthma: Where Are We Heading?

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Over the last decade, an original article on the subject of asthma research has been published, on average, every 3 hours. The investment in tens of thousands of publications, not to mention the hidden cost of studies commissioned by the industry but never published, can only be guessed at. The scientific attention focused on asthma is a clear indicator of the importance of the problem. The prevalence of asthma in children aged 13-14 years ranges between 6% and 10% in Spain, and between 10% and 14% in Canada and the United States of America; in Australia and New Zealand, the prevalence in this age group has reached 19%.[1] World prevalence for combined children and adult populations is more difficult to ascertain. The fruit of scientific effort in this area has certainly been to provide therapeutic resources that enable patients to control their asthma to a satisfactory degree. Nonetheless, if the aim of research is to progress towards mitigating the problem (or even eliminating the disease), in the case of asthma, nature seems to be one jump ahead of human intervention in terms of its own experiments on our immune system. Asthma prevalence has, in fact, increased steadily in industrialized countries in the last 50 years,[2,3] and this trend is paralleled by a growing prevalence of autoimmune diseases and allergies in general. Although additional data on loss of lung function in asthmatics is required,[4] it would seem that the absolute numbers of patients living with difficult-to-treat asthma, poor quality of life, and at the risk of life-threatening crises may have risen in spite of the treatments available. Scientific data on the mechanisms involved in asthma are being produced at a staggering rate—but the vector space is such that it is difficult to see a convergence of knowledge on the complexity of asthma. There is a general consensus that no clearcut progress has been made in the treatment of asthma since the introduction of inhaled corticosteroids—, but has the situation improved on a general level? We can give better treatment to many asthma patients, but there are also many more patients to treat, including more patients with difficult-to-treat asthma. So, where precisely are we heading with basic research into asthma?

We are living in times of unprecedented scientific challenges and technological advances that were undreamed of just a few years ago. All research fields and disciplines are affected by these developments, and the frontiers of knowledge for asthma are no exception, delineated as they currently are by research into the immunological bases for inflammation and inflammatory regulators, airway remodeling, genetic susceptibility factors, and the role played by environmental factors and lifestyle. Space here does not permit even a brief summary of the current scenario and future direction of the application to asthma of the technological resources available. It is possible, however, to focus on a few developments of particular significance. A cornerstone in the generation of new knowledge of asthma is the use of experimental animal models of the disease. Observations of patients with asthma have led to detailed descriptions of chronic inflammation and cellular and biochemical instigators of inflammation; the many structural changes brought about by respiratory airway remodeling; and, most importantly, the relationship between these phenomena and the clinical picture and course of asthma. Nonetheless, given the obvious restrictions on research in humans, it is impossible to determine the mechanisms involved and their clinical implications with the level of understanding that would enable us both to identify preventative and therapeutic targets and to develop suitable treatments and treatment strategies. Most of the insights provided by animal models have come from experiments with rats and mice, and each of those models has its advantages and drawbacks.[5-7] Using rat models, researchers have been able to induce allergic sensitization, airway inflammation mediated by type 2 helper T cells, early and late allergic responses to bronchial provocation with allergens, bronchial

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hyperreactivity to cholinergic agonists, and structural remodeling. The rat model has also been particularly useful in elucidating the role played by T cells in asthma. Mouse models have been used to develop transgenic animals in which specific genes have been enhanced or inhibited. This technology has been widely exploited in order to study the role various cytokines play in airway remodeling. But a limitation of this line of research is that asthma has not been examined in a suitable immunological context as has been done in the studies on sensitization and bronchial provocation. Irrespective of the model chosen, with its corresponding advantages and disadvantages, information from in vivo experiments is complemented by the large amount of information gained from analyses of biological specimens taken from animals or from humans. This line of research has enabled complex relationships between variables to be explored from the vantage point of respiratory physiology, immunology, cell biology, quantitative analysis of structural change, and gene expression. Numerous specific markers can now be identified using detection technologies based on monoclonal antibodies and signal amplification. These resources are particularly exploited by immunohistochemistry and immunofluorescence applications to lung tissue specimens; they enable a wide variety of phenotypic markers to be identified in the leukocyte subpopulations involved in inflammatory infiltrates, and also help to evaluate changes in airway tissue structure components, such as smooth muscle contractile proteins and the extracellular matrix. Another promising technique is confocal microscopy, which is useful for procedures such as ultrafine optic sectioning at the subcellular level, three-dimensional reconstructions of structures, and high-precision colocalization of markers. Morphometry and stereology assisted by digital image analysis are capable of converting all the resulting morphological information into quantitative data. Another useful technique is laser-captured microdissection, or microscopic preparations that allow selected tissue fragments and even individual cells to be isolated for subsequent analysis. Flow cytometry, which permits cell-by-cell analyses, has a vast number of applications in cell suspensions (whether cultured or obtained directly from animals or humans) and in the isolation of subpopulations according to specific characteristics. Another set of tools facilitates studies of the cell cycle and apoptosis—2 areas of particular importance for understanding the mechanisms involved in tissue homeostasis, tissue damage and repair, and abnormal structural remodeling of the airways. Such studies can be performed on either tissue samples or cell suspensions. Molecular biology has also made available a broad range of tools that are constantly being improved. Applications include qualitative and quantitative analyses of specific gene expression patterns in a range of preparations, and broad explorer arrays that employ DNA chip technology. Beyond mere gene analysis, it is now possible to induce or inhibit genetic expression in cells, tissues, or organs—even in the entire organism. Finally, proteomic techniques have opened the door to the postgenomic exploration of differential gene expression in a variety of products, starting us on a long journey which is likely to contribute significantly to genome sequencing in many species.

Application of these new technologies to asthma is beginning to produce information which not only contributes to our understanding of the pathogenesis of the disease, but also gives us a glimpse of what may become interesting lines of future research in which focused efforts may well lead to important advances. The 20th century saw scientists solve the puzzles of the specific antigen recognition mechanisms that distinguish between what belongs to the organism and what is foreign to it, as well as of the adaptive responses of our immune system and its capacity for memory. Even if hindsight suggests that these advances are insufficient, they nonetheless represent a fundamental pillar in our understanding of asthma. One gap in our understanding of both "intrinsic" and "extrinsic" asthma that needs bridging is in regard to why the adaptive mechanism in our immune system leads to unnecessary and persistent responses in a segment of the population which is growing rapidly and whose growth cannot be explained by genetic susceptibility. Although some tentative answers to this question have been furnished by the hygiene hypothesis, that theory has some weak points.[8] Research into the innate immune system—which is relatively unexplored territory in comparison to the adaptive immune system—is likely to uncover important clues to elements that interfere with the modulation of adaptive immune mechanisms in asthma. It can be speculated, in fact, that the field of immunology will shift its interest towards the innate immune system in the coming years, even outside the setting of asthma. Another event marking the turn of the century is the conceptual shift from inflammation to remodeling. The reasons underlying disruption of repair response and its transformation to abnormal structural remodeling are at the cutting edge of scientific interest in asthma and other diseases, such as atherosclerosis, in which there is an association between chronic inflammation and tissue remodeling. An upcoming focus of attention may well be combined regulation of the cell cycle and apoptosis at a juncture where basic shared mechanisms might give rise to morphogenesis, repair, remodeling, or neoplasia by means, perhaps, of genetic switching that is more subtle than can presently be imagined. Another promising line of general interest is research into the role and function of pluripotential adult stem cells in the repair and remodeling processes; of interest in asthma in particular, are their migration routes, interaction with the immune system, possible recruitment in the airways, and differentiation. It is patently clear that there is no shortage of challenges, that little ground has been covered, and that more research is going on than ever. Nonetheless, sight must not be lost of the fact that research needs to produce results that lead to clear advances in resolving the problem in hand. What is sorely needed at this stage is

to develop a forum for consultation and consensus aimed at producing guidelines for asthma research. Such guidelines, which should be international in scope, would ideally focus asthma research in the coming years by defining specific key questions to be answered. Indeed, the greatest difficulty in science is often that of formulating questions rather than seeking answers.

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