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Allergy and Asthma in Modern Society: A Scientific Approach

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Dedicated to Kurt Blaser

Volume Editor

Reto Crameri *Davos*

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Contents

The Skin

Foreword

Allergic diseases and asthma constitute a growing health care problem, especially in industrialized countries. In spite of marked worldwide variation, the prevalence of symptoms of asthma, eczema and allergic rhinoconjunctivitis is increasing. Although genetic factors defining the atopic background of a population are undoubtedly important, they cannot explain this phenomenon. As the genetic background of a population must be regarded as quite stable over short periods of time, environmental factors must be included to explain the remarkable changes in the prevalence and severity of asthmatic and allergic diseases during the last 40 years. As brilliantly summarized by Platts-Mills et al., environmental factors can influence the spread of these diseases; however, single changes in environmental parameters alone cannot explain the consistency or the scale of the rise in allergy and asthma observed between 1960 and 2000. Our environment is extremely complex, poorly defined and difficult to monitor. However, a direct demonstration of the pivotal influence of environmental factors on the severity of asthma comes from a recent reinvestigation by Schultze-Werninghaus of a very old observation describing the beneficial role of sojourns at high altitude. The therapeutic value of such sojourns for severe bronchial asthma patients is well documented, and there is no scientific reason to doubt it. Obviously, our limited knowledge about host-environment interactions and atopic diseases favored the development of various, more or less attractive hypotheses and theories aiming to explain this phenomenon. Among these, the hygiene hypothesis, discussed by Renz et al., is perhaps the most attractive. According to current scientific views, it tries to integrate the interaction between environmental factors, innate and adaptive immunity into a sophisticated

model. We must realize that the human body is not an isolated system. To survive, we need a continuous selective exchange with our environment, allowing the uptake of essential biovital elements and excretion of unwanted metabolites, but aiming to avoid offending agents. Physical barriers and an orchestrated primary and secondary line of defense are required to allow survival. Skin and mucosal surfaces represent by far the largest interface between a human being and the environment and from this point of view it is not astonishing that the respiratory tract (Simon, Kay), skin (Breuer et al., Santamaría-Babí, Bonini) and digestive tract determine an individual's quality of life. However, other diseases, notably conjunctivitis, an often forgotten disease (Bonini), significantly contributes to the health burden of modern society as well.

Inappropriate immune responses to normally harmless environmental antigens, following, for example, exposure to fungi (Crameri et al.) still represent an unsolved health care problem although our understanding of the structural basis of allergens (Aalberse) and their role in the pathogenesis of chronic allergic diseases (Schmid-Grendelmeier et al.) is rapidly increasing. Complex mechanisms regulate the healthy immune responses to allergen exposure (Carballido et al., Akdis et al.) and it is the long-neglected study of these responses that recently contributed to a better understanding of the orchestrated cascades resulting either in normal, protective, or abnormal, disease-related immune responses. Antigen-antibody interactions at the end of the cascade are relatively easy to access experimentally and, as a consequence, our knowledge about these phenomena is quite advanced. Early, tightly regulated cellular interactions resulting from the complex interplay between cytokines, receptors and small molecules, such as histamine (Jutel et al.), strongly depending on genetic background and environmental influences, determine the immune response initiated and the fate of each single individual. It becomes increasingly evident that such immune responses in allergy and asthma are extremely complex. New global technologies based on gene expression profiling (Schmidt-Weber) and proteomic approaches will be required to integrate our knowledge about molecular and cellular interactions into more complete networks aimed at understanding the pathophysiology of allergy and asthma.

However, there is light at the end of the tunnel. The considerable progress in our understanding of molecular and cellular interactions starts to translate into new strategies to combat allergic diseases (Akdis et al., Achatz et al.). Although many drugs are available to control the symptoms of allergy and asthma, immunotherapy is the only treatment currently able to cure these diseases. Several new treatments have been or will be introduced soon for clinical use and will hopefully strongly improve immunotherapy and benefit the patients.

Kurt Blaser, Director of the Swiss Institute of Allergy and Asthma Research, Davos.

Allergy and asthma are very important diseases, and as a consequence, an overwhelming number of original contributions, reviews and books covering the different aspects of these diseases are published every year. Why a book more about this topic? The answer to this justified question can be found in the introduction by Johannes Ring: Kurt Blaser, the director of the Swiss Institute of Allergy and Asthma Research, celebrated his 65th birthday on June 25, 2005. He dedicated all his life to allergy and asthma research and has become one of the most prominent and appreciated global players in this field. I am convinced that, together with me, all authors of this book and many other scientists worldwide are grateful to him for many exceptional scientific contributions and political fights to speed up progress in a field which, in spite of its recognized socio-economic impact, still lacks the political support to mobilize the financial resources required to satisfy its needs. Thank you Kurt!

I am especially grateful to Thomas Nold and his team for their excellent cooperation in editing this book, to the industrial sponsors and to Johannes Ring who supported the idea from the beginning. Of course, I am very grateful to the authors, who have spent much time for the preparation, revision and final checking of the manuscripts. Finally, a big thanks goes to Rosalina and Danja, the unlucky members of the family, waiting at home until I am back from work every day. I am not so sure that I would have that much patience.

Reto Crameri

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The Magic Mountain of Allergy Research

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Davos (Switzerland) is known worldwide for its healthy climate, its high mountains for skiing and mountaineering, but also for its beneficial effects on health. Although Thomas Mann in his famous novel *Der Zauberberg* ('The Magic Mountain') described these effects sometimes rather critically, many patients undoubtedly achieve cure or significant amelioration for their chronic lung or skin diseases, especially allergies, in the healthy climate of Davos.

Apart from this, Davos has gained international reputation as a center of science. Maybe, its healthy climate also exerts a positive influence on the researchers. When, at the end of the eighties of the last century, the Swiss government decided to found a Swiss Institute for Allergy and Asthma Research ('Schweizerisches Institut für Allergie- und Asthma-Forschung'; SIAF) in Davos, nobody could foresee the future. With the choice of Kurt Blaser as the head of this institute, the officials had a very lucky hand. Within 10 years Kurt Blaser turned the SIAF into one of the leading research centers in allergy in the world.

Kurt Blaser was born in Thun, on June 25, 1940, and started as a laboratory trainee from 1957–1960 at a chemical company in Switzerland where he obtained his diploma working on the synthesis of heterocyclic compounds. He then attended an engineering school, where he graduated in 1965. From 1965 to 1972, he studied chemistry at the University of Bern and became a research assistant in inorganic and then organic chemistry. He was awarded an industrial grant to work at the BASF Company, while preparing his PhD at the Institute for Immunology of Bern (with Profs. de Weck and Schneider) from 1972 to 1975. After obtaining his PhD, he worked as a post-doctoral fellow at the Massachusetts Institute for Technology in the USA from 1975 to 1977 (with Profs. Eisen and Luria); from there he returned to the University of Bern and worked as an assistant researcher from 1977 to 1988 (with Profs. Riva and de

Weck). In 1983 he received his degree of 'Privatdozent' ('Habilitation') to teach experimental cell physiology. In 1994 he was awarded the title of 'Professor' and in 2002 he was elected 'Extraordinarius' at the University of Zürich.

Since 1988, Professor Kurt Blaser is the director of the SIAF in Davos. Kurt Blaser was able to attract excellent people. With his pupils R. Crameri, H.U. Simon, J. Carballido, M. Jutel, C.B. Schmidt-Weber, C. and M. Akdis – just to name some of them – the SIAF soon gained international acceptance and representation at all the major congresses in the field. The list of publications of the SIAF contains several 'citation classics' and reads like a list of milestones in allergy research. Among the best-known results originating from the SIAF are the works on eosinophil apoptosis (H.U. Simon), the cutaneous lymphocyte antigen (CLA) (L.F. Santamaría-Babí), the mechanism of immunotherapy (C. Akdis), keratinocyte apoptosis in eczema (M. Akdis), allergen characterization (R. Crameri), histamine in T-cell regulation (M. Jutel).

The SIAF coordinates the Swiss branch of the Global Asthma and Allergy European Network (GALEN) in the European Centres of Excellence in allergy program.

Kurt Blaser served as member of the Council of the Collegium Internationale Allergologicum (CIA) over 6 years and of the Swiss National Research Council. He also was a research advisor for government research programs, especially in Germany, but also in Austria and other European countries. Kurt Blaser has given input in many of the various centers for allergy research in Germany. With his quiet, professional, sometimes visionary mind and his critical but always inoffensive way, he has had a major influence on allergy research in Europe and in the world.

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Environmental Factors Influencing Allergy and Asthma

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Abstract

Despite the strong and consistent association between immediate hypersensitivity, allergy, asthma and exposure, there is still controversy about the role inhaled allergen plays and about the timing of events related to sensitization. However, IgE antibodies are essential for the asthmatic response and the symptoms are much more closely associated with IgE antibodies to perennial than to seasonal allergens. Although there have been many changes in our environment, none of these alone explains the consistency or the scale of the rise in asthma over the 40 years between 1960 and 2000.

The central question about the role of environmental factors in asthma is to understand their relevance to the increasing prevalence of disease. There are two questions that we need to ask first. Are the patients involved in the increase in asthma (i.e. those who would not have had symptoms in 1950) allergic? Second, are all allergens involved equally? If, as appears likely, the majority of the patients are allergic and multiple different allergens are involved, then there are three types of explanation for the increase in asthma.

Increased exposure due to changes in housing and increased time spent indoors has lead to an increase in the number of allergic patients. The same changes could have led to increased severity of symptoms among allergic individuals.

Alternatively it has been suggested that decreased exposure to farm animals, or decreased early childhood infections could have lead to a nonspecific increase in IgE antibody (IgE ab) responses. Similar effects have been ascribed to decreased helminth infection, increased early antibiotic use, or a decline in hepatitis A infection.