# ASTHMA AND RHINITIS

EDITED BY

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Blackwell Science

# Asthma and Rhinitis

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54 University Street, Carlton,
Victoria 3053, Australia
Arnette SA, 1 rue de Lille, 75007 Paris, France
Blackwell Wissenschafts-Verlag GmbH, Kurfürstendamm 57,
10707 Berlin, Germany
Blackwell MZV, Feldgasse 13, A-1238 Vienna, Austria



First published 1995

Set by Excel Typesetters Co., Hong Kong
Printed and bound in the United States of America by
Rand McNally, Taunton, Massachusetts

95 96 97 98 5 4 3

DISTRIBUTORS:

*North America*
Blackwell Science, Inc.
238 Main Street
Cambridge, Massachusetts 02142
(*Orders:* Tel: 800-759-6102
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Blackwell Scientific Publications Pty Ltd
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*Outside North America and Australia*
Blackwell Science, Ltd
c/o Marston Book Services Ltd.
PO Box 87
Oxford OX2 0DT
(*Orders:* Tel: 0865 791155
FAX: 0865 791927
Telex: 837515)

Library of Congress
Cataloging-in-Publication Data

Asthma and rhinitis / edited by William W. Busse
and Stephen T. Holgate.
p. cm.
Includes bibliographical references and index.
ISBN 0-86542-246-X
1. Asthma. 2. Asthma in children. 3. Rhinitis.
I. Busse, W. W. (William W.) II. Holgate, S. T.
[DNLM: 1. Asthma. 2. Rhinitis. WF 553 A82514 1995]
RC591.A73 1995
616.2'38-dc20

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# Preface

In the past decade, many important advances have occurred to improve our appreciation, perception, and clinical approach to asthma and rhinitis. For example, the prevalence as well as morbidity and mortality have increased in asthma; the reasons for such changes are not established but likely provide key insights into the pathogenesis of asthma. Furthermore, the focus and attention on these respiratory diseases has shifted from acute components of illness to factors which explain and cause their chronic, persistent nature. Moreover, it has become apparent that both asthma and rhinitis are extremely complex disorders and are characterized by multiple processes that are redundant and self-amplifying. This new, and hopefully more correct vision, has arisen because of the availability of more powerful and precise techniques for study, methods to begin to analyze genetic control, and availability of tissues from humans with these diseases. Collectively from all of these advances a picture has emerged which is beginning to demonstrate the elaborate interplay between tissues, mediators, and proinflammatory products to cause persistent asthma and rhinitis.

These advances, discoveries, and new concepts were the impetus for our book. We reasoned it would be helpful for the scientist and clinician to have one text which begins to tackle airway allergic diseases in a comprehensive, detailed manner. Furthermore, it is our hope that an extensive review of factors contributing to and playing in the development of these diseases will also give the reader a greater comprehension of the interwoven nature of response which ultimately leads to asthma and rhinitis. Our contributing authors are expert in their respective areas and international in location. The global approach given to this book is paralleled by the expanding more universal approach to allergic diseases.

The editors are appreciative of the dedication of the authors given to the development of this book, the support from Blackwell Scientific Publications, especially Jackie Egerton, Dr Victoria Reeders, and Coleen Traynor, and the administrative assistance of Reitha Johnson and Chris Vincent.

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# Introduction

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These are exciting times for anyone interested in asthma. Never in history has progress been so rapid or the outlook for future advances so promising. "Revolutionary" is not too strong a term to describe the change in the understanding of the nature of asthma and its pathogenesis that has come from adding the new clinical techniques of bronchoscopic lavage and biopsy and the new laboratory methods of cellular and molecular biology to traditional pulmonary physiology and smooth-muscle pharmacology. "Revolutionary" is also appropriate to describe the recent change in the philosophy of treatment, which comes partly from better understanding of the biology of asthma, with primary emphasis on bronchial inflammation, and partly from behavioral science, which places emphasis not on the process of some arbitrary regime, but on the outcome, controlling the disease, and which places the primary responsibility for achieving this control with the patient. With these changes, the physician's task has become more complicated. Now, the task is not only to diagnose the disease and its severity, to identify the provoking factors, and to recommend treatment, but, equally important, it is to teach the patient how to control the symptoms, prevent acute episodes, be physically active, and lead a normal life.

Although the concept that asthma is a particular variety of bronchitis, an inflammatory disease, had been firmly established by the end of the nineteenth century [1,2], during most of the twentieth century attention focused almost exclusively on "bronchospasm." Physiologists defined the adrenergic, cholinergic, and nonadrenergic noncholinergic innervation of bronchial smooth muscle, and pharmacologists developed and defined the mechanism of action of effective bronchodilators. Bronchial provocation tests with methacholine or histamine allowed recognition and quantification of bronchial hyperresponsiveness. The consequence of this focus on the physiology of airways and the pharmacology of bronchial smooth muscle was the widely accepted definition of asthma, that of the American Thoracic Society, which considered asthma as reversible airway obstruction with hyperresponsiveness, and did not mention inflammation [3]. Only in the last 10 years or so has the importance of inflammation been rediscovered, and now the idea of asthma as an inflammatory disease is fully accepted [4,5]. The hyperresponsiveness and mucus hypersecretion are, at least in part, symptoms of the inflammation [6,7,8]. It has become apparent that, as a screening procedure, tests of hyperresponsiveness have imperfect sensitivity and specificity for the diagnosis of asthma [9]. Not all patients with asthma have hyperresponsiveness, and not all persons who are hyperresponsive have asthma [10].

Soon after Ehrlich's description of staining methods to differentiate among the types of leukocytes and his description of eosinophils, eosinophils were identified in blood and sputum of asthmatic patients [11,12]. In 1908 Ellis [13] studying the pathology of fatal asthma described eosinophils in the bronchial wall as well as in the sputum and blood. Ellis's observations [13] have been amply confirmed [14,15]. Dunnill [15] called attention to the fact that the characteristic mucous plugs that occlude the airways in many fatal cases were not simply a secretion of mucous glands but were a complex exudate that included fibrin and other serum proteins, inflammatory cells and degenerating ciliated epithelium. Naylor [16], in 1962, reported that sputum expectorated during an attack characteristically contained clumps of desquamated epithelial cells, which he called "creola bodies." It is important to emphasize that this chronic inflammation of asthma is a very distinct and specific type of inflammation, and differs in important ways from the inflammation of other chronic lung diseases such as sarcoidosis, interstitial fibrosis, and the chronic bronchitis and emphysema from cigarette smoking. This characteristic pathology of asthma can be summarized as "chronic desquamating eosinophilic bronchitis" [17].

Blood and tissue eosinophilia in asthma is not limited to those cases due to allergy, but is present also in intrinsic asthma, often to a greater degree than in extrinsic asthma. The numbers of eosinophils in peripheral blood correlates with the severity of the disease rather than with the presence or absence of allergy to aeroallergens [18]. But eosinophilia is not universal. The bronchi of some patients who have died suddenly of acute asthma do not have eosinophilic infiltration [19,20].

Eosinophilia, then, as a characteristic of asthma is a useful point for the clinician to consider in diagnosis and management. Is it more? Do eosinophils contribute to the inflammation by damaging the airway epithelium and causing its desquamation? Can consideration of the biology of eosinophils improve understanding of the mechanisms of inflammation in asthma?

The evidence that eosinophils play a central role in the inflammation can be summarized as follows [21].

**1** Eosinophils are present in the epithelium not only in fatal cases of asthma but are present in bronchial biopsies even in relatively mild cases [22–26]. The degree of the eosinophilic infiltration correlates with the severity of the disease and with the degree of bronchial hyperresponsiveness [27].

**2** Eosinophils appear in the airway lumen 24 and 48 h after allergen challenge, especially after endobronchial instillation, and the degree of eosinophilia correlates with increased hyperresponsiveness and appearance of sloughed epithelial cells [28–31].

**3** Eosinophil granule proteins, particularly major basic protein, are localized at the sites of epithelial injury, even though intact eosinophils may be scarce [32].

**4** Eosinophil granule proteins are present in sputum of asthmatics in high concentrations during exacerbations of the disease [33].

**5** Eosinophil major basic protein and eosinophil peroxidase are toxic to respiratory epithelium in culture in concentrations found in asthmatic sputum [34].

**6** Eosinophil major basic protein increases airway contractility in *ex vivo* dog trachea [35].

**7** Preventing influx of eosinophils by monoclonal antibody to endothelial adhesion molecules prevents increase in airway hyperresponsiveness after allergen challenge in monkeys [36].

**8** Eosinophil major basic protein and peroxidase activate basophils, mast cells, macrophages, and platelets [37–39].

**9** Eosinophil major basic protein blocks M2 cholinergic receptors, which likely contributes to its effect in increasing airway hyperresponsiveness [40].

Of course, eosinophils do not suddenly appear in the airways fully armed like Athena from the brow of Zeus. Nor are they the sole inflammatory cells in the airway. What can consideration of the biology of eosinophils add to the overall understanding of the mechanisms of airway inflammation in asthma? Briefly put, eosinophils are born and bred in the marrow, travel a short while in the circulation, and migrate into the tissues, where they mature and die. It is most likely that their primary role in host defense is that, in dying, they release toxic granule proteins that kill metazoan or arthropod parasites which are too large for phagocytosis. Their function in allergic disease and other diseases seems quite similar to parasite killing, except the target cells are the host's own tissues rather than a parasite.

Eosinophils arise from promyelocytes, through the action of cytokine growth factors, which were originally described as products of activated lymphocytes. The cytokines responsible for differentiation into mature eosinophils are chiefly granulocyte–macrophage colony-stimulating factor (GM-CSF) and interleukins 3 and 5 (IL-3, IL-5) [41–43]. Circulating peripheral-blood mononuclear cells contain a population of cells that can differentiate into mature eosinophils; it is not known whether eosinophils differentiate from these precursors in the peripheral tissues.

The factors that govern exit of eosinophils from the marrow into the blood are poorly understood.

However, it has recently been appreciated that recruitment of eosinophils into tissues, including the airways, is controlled by cytokines. Studies on peripheral blood, bronchoalveolar lavage (BAL), and bronchial biopsies of asthmatics have shown that there is a correlation between numbers of activated helper (CD4) lymphocytes and numbers of activated eosinophils, and both correlate with disease severity, which suggests that T-cell products are important [44–46]. These lymphocytes resemble a subclass of rodent CD4 lymphocytes, called helper T-cell subset 2 (Th2), in producing the specific variety of cytokines, IL-2, IL-3, IL-4, IL-5, and GM-CSF, that appear to play an important role in allergic diseases [47]. Cytokines regulate expression of cell-surface receptor ligands, both on eosinophils and on endothelial cells, which localize leukocytes at the site of inflammation and serve to recruit eosinophils to areas of inflammation and enhance their state of activation. In particular, IL-5 stimulates the production of adhesion molecules, such as macrophage surface protein 1 (Mac-1) and very-late-activation antigen 4 (VLA-4) on the surface of eosinophils; and IL-4 elicits endothelial cell production of vascular cell adhesion molecule 1 (VCAM-1), the selectin adhesion molecule that binds VLA-4 [48–51]. Monoclonal antibody to endothelial adhesion molecules prevents the accumulation of eosinophils and development of airway hyperresponsiveness in allergic monkeys challenged with allergen [36]. It is of considerable interest that, during allergic inflammation, intercellular adhesion molecule 1 (ICAM-1) is increased not only on vascular endothelium but also on the basal layer of the respiratory epithelium [52].

*In vitro* studies have shown that the cytokines IL-3, IL-5, and GM-CSF can be regarded as being "eosinophil-active," in that they increase human eosinophil survival and prime eosinophils or potentiate their response to other

stimuli [41–43]. Interferon γ (IFN-γ) also can prolong eosinophil survival and enhance cytotoxicity [53], and tumor necrosis factor α (TNF-α) enhances eosinophil toxicity to schistosome larvae [54]. While these effects have been described *in vitro*, the cytokines closely associated with human eosinophilia *in vivo* are IL-2, IL-5, and GM-CSF. IL-2 is an extremely potent eosinophil chemoattractant, and, when given for malignancies, has been associated with a dramatic increase in circulating hypodense eosinophils, likely mediated through the production of IL-5 [55,56]. In patients with hypereosinophilia, elevated IL-5 levels correlate with the rise in peripheral-blood eosinophils [57]. Furthermore, GM-CSF, when used in association with treatment for hematologic malignancies, is frequently associated with peripheral-blood eosinophilia [58].

The *in vivo* association of eosinophil-active cytokines with asthma stems from work showing that subjects with asthma have more BAL cells reacting with antisense messenger ribonucleic acid (mRNA) probes for certain cytokines (IL-2, IL-3, IL-4, IL-5, and GM-CSF) than do normals subjects [47]. Furthermore, when bronchial biopsies were examined for IL-5 mRNA by *in situ* hybridization, six of 10 asthmatics and no controls expressed IL-5 mRNA [59]. In addition, segmental allergen bronchoprovocation in subjects with allergic rhinitis resulted in elevation of IL-3, IL-5, GM-CSF, and IFN-γ in the BAL fluids after 48 h. The presence of the cytokines correlated with the number of eosinophils recovered [60,61]. In addition, macrophages from the BAL fluid during the late phase produce TNF-α and IL-6 [62]. TNF-α has also been recovered from the BAL fluid 48 h after segmental allergen challenge [63]. Thus, the late phase of the allergic reaction is associated with the liberation of cytokines from lymphocytes and other cells, which activate eosinophils, capture them in the bronchial capillaries, and draw them through the capillaries into the mucosa. Th2-like lymphocytes are not the only cells capable of producing these cytokines; many other airway cells, including mast cells, epithelial cells, macrophages, neutrophils, and eosinophils have mRNA for cytokines and can produce cytokines *in vitro* [64–68]. Which of these cells produce the interleukins that attract and activate eosinophils during the late phase of the immunoglobulin E (IgE)-mediated allergic reaction? The answer is not clear. Mast cells are one possible source [66,69,70]. Th2-like lymphocytes activated by high-affinity receptor for IgE ($Fc_{\varepsilon}RI$)-bearing antigen-presenting dendritic cells are another. Or both types of cells could be contributing.

The final event in the process of eosinophil damage to the respiratory mucosa is degranulation and release of their toxic eosinophil granule proteins. Unfortunately, the molecular stimulus for degranulation *in vivo* is still obscure. *In vitro*, the eosinophil-active cytokines, IL-3, IL-5, and GM-CSF, enhance eosinophil degranulation from several potential physiologic and pharmacologic stimuli [71–74]. Stimulation of degranulation by immunoglobulin complexes is mediated through a pertussis-toxin-inhibitable guanine-nucleotide-binding (G) protein and involves activation of phospholipase C and protein kinase C [73]. Glucocorticoids inhibit degranulation and reverse the degranulation-enhancing activity of cytokines [74]. Glucocorticoids also inhibit cytokine production [75].

Bronchial inflammation is at least in part responsible for the hyperresponsiveness of asthma. Three plausible mechanisms for the increase are the exposure of sensory irritant receptors by the epithelial desquamation [76], the simple geometric effect of swelling of the airway mucosa with narrowing of the lumen [77], and the effect of products of the inflammation on receptors of the autonomic nervous system [40].

Although much has been clarified about the specific variety of eosinophilic airway inflammation called "asthma," many unanswered questions remain. Investigations of the mechanisms of the IgE-mediated allergic reaction, particularly the late phase of the response, discussed in other chapters, has helped explain the eosinophilia of allergic asthma, though many details of the intricate network of intercellular reactions involved remain to be clarified. However, the origin of eosinophilia of nonallergic intrinsic asthma remains an enigma. Presumably, many of the intermediate steps of increased eosinophil production in the marrow, their recruitment into the airways, activation, and degranulation, which are the result of production and actions of interleukins and intercellular adhesion molecules, are similar to the events initiated by allergen–IgE antibody binding. Nonallergic asthma often follows a viral respiratory infection, and the cellular immune responses to the infection presumably include generation of eosinophilic infiltrate, but clues are lacking about the factors that initiate the process in other cases of intrinsic asthma. Another important enigma is the apparent self-perpetuating mechanism operating in eosinophilic inflammation, which, once established, tends to continue indefinitely. For example, asthma following a viral infection may persist for years after the acute infection. Also, repeated exposure to occupational allergens (and presumably other allergens) often leads to chronic asthma, with eosinophilia that continues for years after exposure to allergen has ceased [78].

Quite obviously, the revolution is just beginning. Exciting times lie ahead.

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