

Editorial

Bronchial asthma – no more doubts?

Considerable progress has recently been achieved in understanding asthma, allowing standardized approaches to its diagnosis and treatment (1, 2). But is the problem of asthma completely solved, or do we need further research in the management of asthmatic patients?

Metso et al. in this issue of *Allergy* consider whether laboratory tests and especially markers of inflammation and hyperreactivity can help diagnose early asthma. Their study does not give a clear answer, in view of the methodologic problems encountered as well as the small size of the population sample studied. However, the paper should stimulate reflection and research.

In this editorial, we hope to stimulate reflection and possibly correspondence on the role of inflammation in asthma. In fact, we still wonder whether we should treat inflammation in the same way in all forms of asthma, how early we should use inflammatory drugs, how long we should continue treatment and monitor effects, or, finally, how effective the treatment will be (producing complete recovery or only temporary remission?).

The role of inflammation in asthma

Evidence of the role of inflammation in asthma stems from several research approaches. It has long been recognized in *postmortem studies* that an infiltration of mainly inflammatory cells and eosinophils, mucus plugs, epithelium damage, mucosal edema, thickening of the basal membrane, dilation of blood vessels, and hypertrophy of submucosal glands and bronchial smooth muscle are peculiar features of patients who died from asthma (3). More recently, however, similar abnormalities were also found in *bronchial biopsies* of patients with mild asthma during intercritical phases of the disease (4), suggesting that inflammation is not a feature only of asthma deaths. New *immunohistochemical techniques* using monoclonal antibodies against phenotypic and activation markers of inflammatory cells (5), as well as *electron microscopy* (6) and *in situ hybridization techniques* (7), have also allowed a better definition of the cells and cytokines involved in the inflammatory network of the asthmatic bronchi (reviewed by Kay [8]). Moreover,

bronchoalveolar lavage studies revealed the cells and mediators distinguishing asthmatic from normal subjects and their relationship with increased bronchial reactivity. Finally, *bronchial challenge studies* showed that inflammation persists in asthma also long after the offending stimulus and underlies the persistent hyperreactivity and recurrence of bronchospasm (4, 9). In fact, it has long been known that *pulmonary function studies* often reveal abnormalities even during asymptomatic phases of asthma (10).

This has led to a general consensus on the role of inflammation in asthma (1, 2) and, after so much controversy and debate, to a unifying operational definition of the disease:

Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. This inflammation also causes an associated increase in airways responsiveness to a variety of stimuli.

On the basis of this definition, we should like to consider some aspects which, in our opinion, still deserve discussion and research.

Asthma is a chronic inflammatory disorder of the airways

Is there a unique inflammation in the different etiologic forms of asthma?

By the classification of Rackemann (11), asthma has long been divided into two different etiologic categories: 1) extrinsic asthma, which affects young patients, is caused by allergens, is based on an IgE-mediated mechanism, is referred to allergists, is diagnosed by allergy tests, and is often treated with hyposensitization only; and 2) intrinsic asthma, which affects mainly adults over 40 years of age, is caused by heterogeneous factors, is mainly based on an autonomic imbalance, is referred to pneumologists, is diagnosed by pulmonary function tests, and is often treated with bronchodilators only.

According to this etiologic categorization of the disease, other "causes" of asthma – such as infections, exercise, aspirin, psychologic stimuli, or occupational exposure – were subsequently considered "indicative of etiologic information, placing the patient in a compound diagnostic category".

Today, chronic inflammation and bronchial hyperreactivity are considered the basic abnormalities in asthma. Once that inflammation and bronchial hyperreactivity are present, various factors can trigger asthma symptoms, independently of the "cause" of the disease. This new view of asthma has led to a unifying concept of the "disorder" (i.e., chronic inflammatory), with substantial improvement in the treatment of asthmatic patients. In fact, most patients are successfully cured by anti-inflammatory drugs (1, 2).

But is there a unique inflammation in all the different etiologic forms of asthma? Or, are there preferential pathways of activation of the inflammatory cascade in the different etiologic forms of asthma or even in different patients with the same type of asthma? In other words, is asthma, pathophysiologically a disease or a syndrome? These questions have not only theoretic but also practical interest. In fact, while the present anti-inflammatory therapy – with steroids, for instance – has a widespread effect on cells and mediators, we might expect to develop a more selective anti-inflammatory treatment depending on the type of cells and mediators preferentially involved in the specific case. We may need specific antimediator or anticytokine drugs, which might also be useful to reveal, in experimental inhibitory challenge studies, the pathogenic role of the relative targets in different types of asthma.

The evidence of different types of inflammation in different forms of asthma is scarce and poorly investigated. However, a different modulation by T cells and/or cytokines present in the micro-environment of inflammatory processes has been postulated in different forms of asthma (12). In fact, while a typical subset of TH2 cells producing interleukin (IL)-3, IL-4, IL-5, and GM-CSF causes induction and modulation of inflammation in allergic asthma, in intrinsic asthma, peculiar T-cell clones producing IL-3 and IL-5, but not IL-4, have been identified. This might explain the similar effect on growth, priming, and activation of primary and secondary effector cells but the different effect on IgE production. Interestingly, however, not only are eosinophils a common feature of all types of asthma, but also total IgE is increased in intrinsic asthma (13). This suggests that the major difference between allergic and nonallergic asthma is the ability to recognize only allergen and mount a specific response in subjects with the same TH cell and

cytokine profile, causing polyclonal IgE (and IgG4), activation as well as upregulation of inflammatory cells.

Moreover, *neural influences* can also differ depending on the different triggers of inflammation and asthma (14), or, finally, preferential *effector pathways* might be involved in different forms of asthma and be better elucidated by fibroscopy challenge studies. In fact, the complex network of cells and mediators involved in regulatory, as well as in primary and secondary effector, mechanisms might permit a large variety of pathophysiologic options. We propose that after the unifying effort made in past years, we should now try to reanalyze the heterogeneous disorder of asthma.

This inflammation causes symptoms in susceptible patients

Is asthma inherited or induced by inflammation?

It has long been recognized that asthma has a constitutional basis. However, most past studies do not distinguish between predisposition to atopy and predisposition to asthma. Recently, the existence of a dominant gene for atopy on chromosome 11q (15) caused extensive discussion and controversy, while the genetic control of bronchial hyperreactivity is still obscure. It seems clear, however, that asthma is subject to complex polyfactorial control and that each of the variables of asthma, and of allergic diseases in general, is also subject to polyfactorial control.

Among genetic factors which influence asthma, special attention should be given to the following:

- 1) the genes controlling the specific response to allergen epitopes, located in the MHS and linked to HLA antigens (16);
- 2) the cytokine gene cluster, located on chromosome 5, regulating the Ig switch to IgE and IgG4 through IL-4 as well as the growth, activation, and functions of modulatory and effector cells through IL-3, IL-5, and GM-CSF (The overexpression of the products of this genome region might be the fundamental feature of all "allergic diseases", including both forms with specific IgE antibodies and those with no detectable specific IgE response.);
- 3) the still unexplored area of genes controlling tissue response.

It is also conceivable that various environmental factors influence the phenotypic expression of these genes, such as the quality, type, route, duration, and intensity of exposure to allergens as well as to other substances capable of inducing inflammation and tissue damage (17).

Can asthma be cured completely?

If asthma is acquired inflammation, it might be completely cured by adequate anti-inflammatory treatment. However, basic abnormalities may persist even with effective treatments; to paraphrase the aphorism, *semel asthmaticus, semper asthmaticus*. Follow-up studies of asthmatic patients treated for up to 2 years with topical steroids indicate that bronchial hyperreactivity often persists even after the disappearance of symptoms, thus suggesting the existence of basic or irreversible lesions not susceptible to changes after therapy (18). "How reversible is reversible asthma?", and "can asthma be cured?" are questions still awaiting definitive answers.

Do relationship inflammation and airways responsiveness have a cause-and-effect?

Several observations suggest that inflammation in the bronchi is closely related to airways responsiveness. However, airways responsiveness without inflammation and inflammation without airways hyperresponsiveness have also been documented (19). Clinically, the relationship between inflammation and asthma entails the problem of identifying *diagnostic markers of the intensity of inflammation*. In fact, immunologic diagnosis of asthma has long been based on etiologic tests (such as skin tests and IgE determination) to confirm or to exclude the allergic nature of the disease.

Several substances are possible markers for monitoring inflammation in asthma at different tissue levels and by different techniques. However, serum levels of eosinophil products have received particular attention in view of the easier performance of the tests as well as of the primary role of eosinophils in inflammatory processes in asthma (20). Studies on the relationships between some mediators of inflammation – such as tryptase, eosinophil cationic protein, myeloperoxidase, and basophil histamine release – and bronchial reactivity to histamine, as well as other studies, show promising advances in this area. More extensive prospective investigations, however, are needed for more accurate pathophysiologic diagnosis and monitoring of the asthmatic patient.

In conclusion, in asthma, as in many other diseases, advances in knowledge solve many problems but also raise new questions in the search for truth. Prof. Sergio Bonini

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