REVIEW ARTICLE

Scientific Impact of the Asthma Awareness Year, 2003: Analysis of Publications in ARCHIVOS DE BRONCONEUMOLOGÍA

A. de Diego-Damiá and E. Martínez-Moragón

Servicio de Neumología, Hospital Universitario La Fe, Valencia, Spain.
Servicio de Neumología, Hospital de Sagunto, Sagunto, Valencia, Spain.

In recent years, some Spanish pulmonologists have felt that more research in some respiratory diseases such as apnea and sleep disorders and in treatment of noninvasive respiratory support, or the advances in anti-infective drugs implied a certain lack of interest in other airway diseases such as asthma. This general tendency is reflected in a lower number of presentations about asthma at both regional and national congresses in Spain and fewer original articles on asthma submitted to ARCHIVOS DE BRONCONEUMOLOGÍA. It is also true that significant progress has been made in determining the pathogenesis of asthma in last 20 years and that effective treatments are available which, in theory anyway, are able to “control” the disease. As a result, even though health care professionals may be less concerned about asthma, it remains one of the biggest worldwide health problems with a large social and economic impact on the population. The prevalence of asthma (4%-5% among adults and 6%-8% among children) is increasing in association with our western lifestyle, particularly in urban areas. Furthermore, 30% of asthma patients are thought to be unaware that they have the disease and the quality of life of 70% of those diagnosed with asthma deteriorates due to repercussions of the disease. Pulmonologists must therefore remain vigilant and be aware of that continued effort will be needed over the years if the outlook is to change.

Pharmacoeconomics studies make for disheartening reading. Asthma is estimated to account for between 1% and 2% of the total health care budget in the United States of America and European countries. Half the costs related to asthma can be considered indirect and the other half direct. The largest component of the direct costs (around 37%) is expenditure on drugs, followed by hospital costs (30%). Studies of overall asthma-related costs have not been conducted in Spain: only partial data are available from a study in the district of Osona in the province of Barcelona. In that study, indirect and direct costs both contributed 50% each to the overall cost. Expenditure on drugs accounted for 45% of the direct costs and hospital costs accounted for a further 32% (75% for hospital stays, 15% for emergency room services, and 10% for attendance at external clinics). The cost of the disease increased exponentially with increasing asthma severity. The cost of moderate asthma was twice as high as that of mild asthma, whereas the cost of severe asthma was 5 times that of mild asthma. Thus, patients with severe asthma, who represented 14% of asthma patients, accounted for 50% of the total cost of the disease. The sum of the main indirect costs (disability benefit and sick leave) and hospital costs (failure of outpatient treatment) accounted for around 70% of the total, giving an indication of the costs generated by poor control of the disease. These figures suggest that more should be done and that we still have a long way to go before achieving the goal of having well-controlled patients with a normal quality of life.

In 2002, the board of the Spanish Society for Pulmonology and Thoracic Surgery (SEPAR) took the decision to designate 2003 as the Asthma Awareness Year, with the basic aim of spreading scientific knowledge about the disease among health care professionals at different levels of care and of raising public awareness of the disease. The Asthma 2003 Committee, with links to the Respira Foundation, was set up with the aim of proposing activities to help achieve these objectives. The first decision of this committee was to draft a Spanish consensus document with the collaboration of the different scientific societies representing health care professionals involved in the treatment of asthma patients. The document was to provide an update of the current knowledge of the disease, with reference to the situation in Spain. As a result, the “Asthma Management-Spanish Guidelines” (GEMA in the Spanish abbreviation; www.gemasma.com) were published. Under the auspices of SEPAR, in addition to pulmonologists, primary health care physicians, pediatricians, nursing staff, and, occasionally, other specialists also involved in asthma such as
The Asthma Awareness Year has, 2 years later, left us with the important interdisciplinary document GEMA, which we believe is well known among a large number of physicians and which has been of practical use in health care for many of them. Time alone will tell whether the recommendations will continue to be followed and the ultimate objective of improving management of the disease is achieved. In our opinion, the Asthma Awareness Year has nevertheless served to stimulate Spanish pulmonologists to study the disease and publish their results.

This review aims to analyze the true short-term impact (that is the impact between January 2003 and July 2005) of the Asthma Awareness Year on publications appearing in ARCHIVOS DE BRONCONEUMOLOGÍA. The members of SEPAR’s Asthma Assembly are well aware that it is still early, and only a longer period can truly reflect the educational efforts made in 2003. The review will endeavor to summarize editorials, reviews, and original articles published in these 30 months, and to provide an overview of the main topics covered by the journal.

In the period covered by this review, a total of 20 articles directly related to asthma have been published (Table 1). The types of article are as follows: 6 editorials,4,6-10 4 review articles,11-14 7 original articles,15-21 1 case report,22 and 2 letters to the editor (Table 2).

A special supplement was also published.3 In addition to these, articles published in annual supplements that include both annual reviews of hot topics in pulmonology and summaries of presentations made in certain meetings have also been published as special supplements. The topics covered in these articles, as we shall see later, are varied and range from clinical studies (management of asthma exacerbations, therapeutic

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<thead>
<tr>
<th>Year of Publication</th>
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<td>2005 (January-July)</td>
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TABLE 1

Annual Distribution of Asthma-Related Publications
in ARCHIVOS DE BRONCONEUMOLOGÍA

<table>
<thead>
<tr>
<th>Type of Article</th>
<th>No. of Publications</th>
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<tr>
<td>Editorial4,6,10</td>
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<td>7</td>
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<tr>
<td>Case Reports22</td>
<td>1</td>
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<tr>
<td>Letters to the Editor23,24</td>
<td>2</td>
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<tr>
<td>Special Reports3</td>
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<tr>
<td>Total</td>
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TABLE 2

Distribution of Publications on Asthma Between January 2002 and July 2005

epidemiologists, allergists, or exercise and sports physicians, provided input during the formulation of the document. Patients were also consulted, and an association for asthma patients participated officially in drafting the document.

GEMA is an update of the current knowledge on asthma, adapted to the actual situation in Spain in terms of resources, drugs, and health care structure. The guidelines also consider epidemiological and clinical data from Spain and, of course, the level of evidence is provided for all statements and recommendations. The guidelines were designed to provide a practical tool for those who treat asthma patients, whether as family physicians, pediatricians, or pulmonologists. A concise paperback version has been published to speed up consultation and decision-making and a version in Catalan is available for the benefit of some Spanish autonomous communities. Finally, a version has been produced for patients and families with the aim of providing patients with the information that they need about asthma. This version, known as “GEMA for patients, family members, and friends,” represents a novel development as other guidelines and consensus statements published up until present have not extended to versions aimed at the general public.

Once the document had been drawn up, it was important to ensure that it reached as wide an audience as possible, particularly among health care professionals, but also among patients. GEMA was presented at the SEPAR National Congress in Zaragoza in 2003 and mailed to SEPAR members. An electronic version was published on the web site of the Society and on a web site created specially for GEMA, and also in the SEPAR’s journal.5 In the last quarter of 2003, local meetings aimed mainly at primary health care physicians were held with the support of regional scientific societies to encourage study of GEMA and to stimulate debate about asthma. Members of the Asthma 2003 Committee played an active part in these meetings and tried to involve as many local asthma experts as possible.

The public was informed that SEPAR had decided to dedicate 2003 to asthma in a series of press conferences. The following consistent general message was conveyed: “Asthma is a chronic disease that can currently be treated effectively, particularly when diagnosed and treated early. It is important to visit your family doctor when you suffer the first symptoms (dry cough, chest sounds, breathing difficulties) and to keep on taking the treatment as prescribed in the knowledge that this will allow you to lead a normal or, if the disease has progressed, an almost normal life, with very few (almost insignificant) side effects due to treatment.”

The latest attempt to increase dissemination of knowledge of this disease was the creation of an award for written and audiovisual journalism, an award for children’s drawings, and a youth award for writing. The children’s and youth awards were publicized in schools to encourage debate about asthma in the classroom.
The first article covered by this review was an editorial entitled “Childhood and Adult Asthma,”21 published in the February 2003 issue of ARCHIVOS DE BRONCONEUMOLOGÍA. That editorial looked at epidemiological studies of the transition of cohorts of asthmatic children into adulthood and their repercussion for the incidence of asthma in adults. The most important studies, such as the one published by Sears et al.,22 with a follow-up of 35 years, or the one by Tasmania, with a similar follow-up period, are contradictory in that they attribute varying importance to asthma symptoms in childhood as predictors of adult asthma. The editorial also analyzed the prognostic factors for persistence of childhood asthma into adulthood, such as bronchial hyperreactivity or the age of onset of symptoms, and concluded that, at present, the capacity of these variables to predict asthma remains uncertain.

In the same issue, Cortijo,7 from the Department of Pharmacology of the Universitat de Valencia, Spain, published an editorial on what information animal models of asthma can provide and the limitations of such models. The advantages of these models lie in the possibility of manipulating environmental and genetic variables, and in determining short-term histopathological changes. Unfortunately, no experimental models are available at present that closely simulate the conditions of human asthma. The models of acute bronchoconstriction, late reaction, and hyperreactivity covered by the editorial are described extensively and in detail, as are the models for active and passive sensitization. According to the author, the murine experimental model is currently the most widely used and the one that most closely resembles human asthma—an affirmation that was corroborated in a subsequent review.

An interesting study by Martínez-Moragón et al.15 dealt with the perception of dyspnea induced by bronchoconstrictors in the laboratory. The same group complemented these findings with further studies27-29 on important issues such as the perception of dyspnea in chronic asthma. The initial study tested the hypothesis that perception of dyspnea induced by bronchoconstriction varies from patient to patient. Such differences in perception could explain the different usage of health care resources or point to why the disease is more difficult to control in some patients. The authors attempted to group patients into clinical, functional, and psychological groups that allow the perception of dyspnea to be more accurately identified. The sample comprised 153 patients with stable asthma and the variables studied were concentration of bronchoconstrictor able to induce a decrease in baseline forced expiratory volume in 1 second (FEV₁) of 20% (PC₂₀), the severity of dyspnea on the Borg scale on reaching PC₂₀, and the differences in this scale between the start of the test and after reaching PC₂₀. According to the study, the most significant factors influencing perception of dyspnea are, on the one hand, anxiety and, on the other, the baseline dyspnea threshold. The authors found that 13% of their patients could be considered poor perceivers, whereas 25% were considered over perceivers. In addition, 15% were classed as abnormal perceivers; that is, dyspnea improved despite greater bronchoconstriction.

In a subsequent study,20 the authors examined this hypothesis in more detail by analyzing whether the capacity for discerning acute bronchoconstriction varied according to groups classified as poor, normal, or over perceivers for baseline severity perception. In a population of 99 patients, baseline score on the Borg scale showed limited agreement with change in both the over-perceiver group and in the poor-perceiver group, but agreement was better for those with normal perception. According to the authors, these results have important practical implications, as self-treatment programs based on lung function are less likely to be successful in poor or over perceivers. Additionally, it is important to identify these patients when treating some cases of asthma that are difficult to control.

In May 2003, an original article published by Pacheco et al.24 explored an idea put forward many years ago by Burrows and co-workers.30,31 According to this idea, some patients with COPD present similar characteristics to those of patients with asthma, such as the presence of bronchial hyperreactivity and atopy, and elevated serum levels of immunoglobulin (Ig) E. The prognosis for this subgroup of patients, described by Burrows and co-workers as having “asthmatic bronchitis,” was different to that of the other groups. Thus, Pacheco et al studied the prevalence of allergic sensitization and the presence of bronchodilator responsiveness in a population of 23 pulmonary emphysema patients who were scheduled for lung transplants. The variables analyzed in this group were percentage of eosinophils in blood and sputum, total and specific serum IgE levels, and the bronchodilator test.

Surprisingly, characteristics that could be considered asthmatic were found in a high percentage of these patients—between 47% and 68% depending on which study variable was being analyzed. Significant correlation was also found between variables, such as eosinophilia and bronchodilator responsiveness. Three or more positive variables were considered to constitute an asthmatic profile, a condition met by 48% of the study population (99.9% confidence interval, 18%-80%).

In July 2003, Muñoz et al.25 published the case report of a 26-year-old patient who developed occupational asthma after starting work in a fish-processing factory.
where plastic sheets were used. Her asthma was probably triggered by exposure to polyvinyl chloride, although the authors cited other potential factors. Given the widespread use of this product, its possible relationship with the development of asthma should be taken into account.

In January 2004, Rodrigo et al\textsuperscript{13} published a very interesting review that reflected on whether fatal or near-fatal asthma should be considered a well-defined clinical condition of greater intrinsic severity or merely a set of factors that had been poorly managed and were therefore modifiable. Studies that use the concept of fatal asthma, which ends the patient’s life, and near-fatal asthma, defined as the appearance of events such as cardiorespiratory arrest, acidemia, or hypercapnia, or the need for orotracheal intubation or mechanical ventilation, are becoming less common in the literature, even though the conditioning factors, disease course, and prognosis are still not well known. In the review, the authors analyzed and described all the risk factors related to these events, as well as the pathophysiology, course of the disease, recognition, and treatment or prevention of exacerbations. The section dedicated to appropriate management and treatment of exacerbations suggests that each one should be considered potentially fatal and measures should be taken accordingly. Appropriate management would include objective evaluation of the severity of the exacerbation and treatment administered in accordance with the situation of the patient. Furthermore, such treatment would often include the regular use of inhaled corticosteroids.

Giner et al\textsuperscript{16} published a study with important practical implications in March 2004. The study investigated the preferences of asthma patients when choosing dry powder inhalers and factors that influenced their choice. The authors studied a group of 30 asthma patients who had been treated with dry powder inhalers for at least 6 months. Patients were instructed in the correct use of the 3 inhalers studied (Accuhaler, Turbuhaler, and Easyhaler). After randomization, the patients used each of the 3 inhalers for 1 week and rated different aspects of their use on a scale of 0 to 10. The final scores obtained showed that patients preferred the Easyhaler model.

The editorial “Zoonoses and Asthma,” by Carrillo and Castillo,\textsuperscript{8} published in June 2004 reviewed the evidence for a relationship between helminth infection and atopy, as well as the presence of respiratory symptoms such as wheezing. Intestinal infections by helminths could be related to atopy through a mechanism of polyclonal stimulation of IgE synthesis.\textsuperscript{32}

Other studies, however, have considered whether such infections could actually provide protection against the appearance of asthmatic symptoms,\textsuperscript{33} an apparent contradiction that could be partly explained by differences in methodology. Also, more than one type of helminth infection might be present, and only the predominant antigen might modulate response. The findings from a study of patients on the Island of Gran Canarias, where there is a high rate of atopy, did not seem to confirm the protective effect in children infected with \textit{Toxocara canis}, given that children with asthma had higher antihelminth IgG levels than the group of children without asthma.

In August 2004, Bazús,\textsuperscript{4} the coordinator of SEPAR’s Asthma Assembly, published an editorial on what SEPAR’s designation of 2003 as the Asthma Awareness Year has meant. The aims of the year-long project were clear: to encourage debate and improve the scientific knowledge of the health care professionals, as well as to raise awareness of the disease among the general population. With regard to these aims, the author went over how GEMA, an updated set of guidelines adapted to the situation in Spain, was formulated by consensus among scientific societies interested in asthma with the collaboration of the patients themselves. The guidelines, which were published in their entirety in Supplement 5 of 2003, included not only a review of the epidemiology, pathophysiology, pathogenesis, and diagnosis of asthma, but also, and more importantly, special situations in which asthma is hard to control and childhood asthma.\textsuperscript{5} Bazús reflected on the successes and failures of the Asthma Awareness Year, with particular consideration, later reinforced by López\textsuperscript{14} in another superb review, of how our attitudes and the physician-patient relationship have changed and the influence that this change should have on the lines of investigation, collaboration, and participation of all those who work with asthma.

Valero and Serrano\textsuperscript{9} of the Allergy Unit of the Hospital Clínic de Barcelona, in an editorial published in September 2004, analyzed the effectiveness of allergen avoidance measures aimed at reducing the allergen load and the clinical manifestations of house-dust-mite allergy. The usefulness of these measures was reviewed extensively, both in primary and secondary prevention, and the authors concluded that there is no evidence in favor of these avoidance measures despite their being widely prescribed in daily clinical practice.\textsuperscript{34,35} Nevertheless, in view of experimental difficulties, the authors propose that these measures should be applied on an individual basis and that the cost-benefit should be assessed.

In the same issue, Romero\textsuperscript{11} reviewed the relationship between asthma and cigarette smoke in terms of both its impact as an inductive factor and its effect on asthma exacerbations. The findings from a number of studies on the incidence of passive smoking among children were analyzed in detail. Perhaps the most important of these studies was the ISAAC study,\textsuperscript{36} which included results from Spain.\textsuperscript{37} Data for adults from multicenter studies such as the EGEA study\textsuperscript{38} and various meta-analyses were presented to assess the probability of smokers developing asthma. The effects on lung function of environmental exposure to cigarette smoke have been analyzed mainly in epidemiological studies done in children, although the methods, particularly with regard to duration of follow-up, and the findings of these studies vary widely. This

interesting review article concludes that there is evidence that parents who smoke directly influence the respiratory health of their children, predisposing them to the appearance of childhood asthma. In cases of childhood asthma, passive smoking favors the onset of more severe asthma. The relationship is not so clear in the adult population, although evidence does suggest that the clinical course of the disease is worse for asthmatic smokers.

In September 2004, the Spanish Group of European Community Respiratory Health Survey (ECRHS)17 published a new finding from their large study. The study analyzed the association between the ratio of forced midexpiratory flow (FEF25%-75%) to forced vital capacity (FVC) and bronchial hyperresponsiveness. FEF25%-75%/FVC was considered an indication of airway-lung size dysanapsis. The cross-sectional study analyzed a population of 2647 adults (aged 20-44 years) from 5 different regions of Spain (Albacete, Barcelona, Galdakao, Huelva, and Oviedo). In accordance with the model already published with the findings of the ECRHS, the authors found a significant association (odds ratio, 0.97; 95% confidence interval, 0.46-0.98) between FEF25%-75%/FVC and the dose of methacholine able to induce a 20% decrease in baseline FEV1 after adjusting for the FEV1 value, smoking habit, atopy, geographic region, age, sex, IgE levels, and respiratory symptoms. Thus, lower FEF25%-75%/FVC was associated with higher risk of presenting bronchial hyperreactivity.

The March 2005 issue of the journal contained an extensive review article covering basic research with clinical applications. This research has demonstrated pathogenic similarities between allergic asthma in humans and models of asthma induced in the mouse.12 The murine model for allergic asthma is dealt with extensively, and topics ranged from the mechanism of induction after administration of ovalbumin to an explanation of all the effects produced. Bronchial hyperreactivity, bronchopulmonary inflammation, and structural changes that occur in the murine model and imitate what is observed in human asthma, are described in great detail with reference to histopathology and analysis of inflammatory cells in bronchoalveolar lavage. The main differences between the murine model and human asthma lie in the apparent lack of genetic interference in mice, as well as the lack of importance of IgE as a trigger of asthma in the murine model.

Two months later, de Miguel10 reflected on the pharmacoeconomics of both asthma and COPD in Spain—that is, the economic impact of direct and indirect costs of the 2 diseases. He reviewed some of the published articles, deliberated on the efficacy of some treatments, and invited readers to consider the efficiency not just of the drugs, but also of the diagnostic or therapeutic interventions.3,38-40 This approach can boost not only the overall efficiency of the Spanish health care system but also, more importantly, improve control of the disease.

ARCHIVOS DE BRONCONEUMOLOGÍA published a study of great clinical interest on the prevalence of hyperventilation syndrome in patients treated for asthma in a pulmonology clinic.19 The authors collected the answers to the Nijmegen questionnaire from 157 asthma patients. They found that 36% of the patients suffered from hyperventilation syndrome and 2% from panic disorders. The frequency was higher in women and the score on the questionnaire was related to the baseline severity of dyspnea and measures of sensitivity to anxiety.

Recently, Belda et al33 attempted to quantify the changes in vascular permeability and edema of the bronchial mucosa in patients with asthma exacerbation by studying the relative index of sputum-to-serum levels for proteins such as albumin or α1-macroglobulin. They analyzed 3 subject groups: healthy nonsmokers, patients with stable asthma, and patients with a mild-moderate exacerbation. An exacerbation was defined as worsening of symptoms over at least 48 hours, accompanied by a 20% decrease in FEV1. An induced sputum sample and a peripheral blood sample were collected from all patients. The study variables were total and differential cell counts, and protein levels in sputum and serum supernatant. The authors described a significant increase in the relative index of sputum-to-serum levels for albumin in the 3 groups, but mainly in the group with asthma exacerbations compared to the control group. No differences in macroglobulin values were found among the groups. The authors found no significant relationship between eosinophils and the aforementioned relative indices, even though there was an association between sputum neutrophilia and the relative index of albumin sputum-to-serum levels. Among the conclusions drawn from the study, it was mentioned that albumin is a better marker for extravasation than macroglobulin and that albumin bears a certain relation to inflammation and the severity of obstruction.

The Spanish centers that participated in the COAX study, conducted in 8 European countries, on costs and management of asthma exacerbations presented the Spanish results in this journal.21 Six Spanish hospitals participated in the observational study, which included 126 consecutive patients who attended the emergency room or who made an unscheduled visit for an asthma exacerbation. Patients were stratified according to the severity of the exacerbation and the disease, and the direct and indirect costs were analyzed from a social perspective. Direct costs were taken to be those arising from medication, visits to the clinic, diagnostic tests, and therapeutic devices. Indirect costs were calculated from the time off work. The authors found that up to 41% of the patients had not been treated for their exacerbation before attending the hospital and that 44% required admission to hospital. A mean number of 8 diagnostic tests were carried out per patient (72% required chest x-rays and 67% required arterial blood gas analyses), whereas peak expiratory flow was only
measured in 33%. The rate of readmission was 10% after 8 weeks, and the mean number of working days lost was 19.5. The mean cost of the exacerbations treated in the hospital was 1555.7 € (95% confidence interval, 1237€–1907€), 93.8% of which corresponded to direct costs and only 6.2% to indirect costs. The authors found a relationship between severity and cost—persistent severe asthma is 2.2 times more costly than intermittent asthma. Interestingly, the authors found that long-acting β₂-adrenergic agonists were underused and only 61% of the patients with a severe exacerbation received treatment with inhaled corticosteroids. In the emergency room, only 50% to 60% of the patients received a written plan for self-management. The study was particularly pertinent because of the paucity of information on the costs and management of asthma exacerbations in Spain. The main conclusion was that a high percentage of asthma exacerbations are due to the lack of preventative treatment and self-management plans.

A review by López dealt with approaches for improving adherence to therapy among patients with asthma, a topic related to the conclusions of the previous study. The author of this review provided an extensive description of the reasons for poor adherence, the types of poor adherence (erratic, unintentional, intentional), and the variables that might modify behavior. In accordance with the model described, reasons for poor adherence can be divided into 3 broad groups, depending on whether they are related to the patient, to techniques used in the intervention, or to how an intervention program is structured. Factors attributable to the patient include knowledge of the disease, motivation or willingness to change behavior, the personality of the patient (self-sufficiency, anxiety-depression, and learned helplessness), and differences in the state of health or severity of the disease. The author described in detail the set of direct and indirect techniques that should be used in the educational programs in order to influence the behavior of the patient and so encourage adherence. Important direct methods include an effective medical interview, enhancement of verbal and nonverbal communication skills, and encouragement of interactive communication.

As the author pointed out, the relationship between the physician and the patient is the most powerful method for modifying behavior and this relationship should be based on trust, respect, exchange of information, and collaboration with the patient. Improvement in the patient’s knowledge of the disease is another procedure—an indirect one—that has been shown to be effective, though to a lesser extent. Information should be brief, simple, and up-to-date. Direct techniques, such as medical recommendations or joint decision-making, have not been shown to be effective. Finally, the author made recommendations about the alternative ways to change attitudes related to poor adherence. These can be summarized in the following categories: a) determining the goal of behavioral change; b) teaching the patient—

the targeted skill for example; c) encouraging the patient to practice the skill; and d) giving the patient opportunities to talk about and analyze the results.

During the last 2 years, the journal has published an annual issue covering so-called hot topics. These issues aim to provide an update of aspects considered relevant to pulmonology. This form of continuing education could hardly exclude topics related to asthma, particularly after the 2003 Asthma Awareness Year. In 2003, Pellicer reviewed the evidence in favor of early treatment of asthma and, in 2004, Belda analyzed the importance of inflammation in asthma, both for diagnosis and to mark disease course.

An assessment of the quality or future impact of these studies lies outside the scope of this review. The more modest aim has been to offer an overview of what the Asthma Awareness Year 2003 has meant for publications in this journal. Nevertheless, it would be unfair not to finish by expressing the hope that these years have changed the course of a SEPAR assembly that was in need of revitalization. The designation of the Asthma Awareness Year by SEPAR has been a crucial factor in renewing interest in this disease.

REFERENCES