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FIXED AIRFLOW LIMITATION CAUSED BY COPD OR ASTHMA: FROM DEFINITION TO MANAGEMENT

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ABSTRACT. PATIENTS WITH FIXED AIRFLOW LIMITATION are often classified as chronic obstructive pulmonary disease (COPD), and some international guidelines recommend classifying asthma with fixed airflow limitation as COPD. Indeed, both COPD (induced by smoking or other noxious agents) and asthma may be associated with a decline of lung function that should cause fixed airflow limitation. In the presence of fixed airflow limitation, patients are often diagnosed COPD, even if the differential diagnosis between asthma and COPD in these patients may be important as the natural history as well as the response to treatment are different, depending on whether fixed airflow limitation is due to asthma or COPD. The assessment of patients presenting with fixed airflow limitation has recently highlighted that airway inflammation is markedly different in asthma and COPD although characterized by the same degree of airflow limitation. Thus, asthma with fixed airflow limitation maintains the same pathological characteristics as asthma with completely reversible airflow limitation. In conclusion, subjects with asthma have distinct characteristics compared with subjects with COPD. Despite the presence of fixed airflow limitation both patients should be properly identified and treated.

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1. DEFINITION

Patients with fixed airflow limitation (or non-reversible airflow limitation) are often grouped under the general heading of Chronic Obstructive Pulmonary Disease (COPD), and international guidelines [1] recommend classifying asthma with fixed airflow limitation as COPD. Although asthmatic patients with fixed airflow limitation are often diagnosed as COPD, the differential diagnosis between asthma and COPD in patients with fixed airflow limitation may be important, as the natural history [2] as well as the response to treatment [3] are different, depending on whether fixed airflow limitation is due to COPD or asthma. In fact, although COPD and asthma share two common features, i.e., airflow limitation and airway inflammation, they are two distinct chronic respiratory disorders [4,5].

For clinical purposes, COPD has a functional definition, based on a spirometric assessment, and is defined as a syndrome characterized by airflow limitation that is not fully reversible (fixed) (post-bronchodilator FEV1/FVC < 70%) and progressive. This syndrome generally occurs in a subject with a current or previous history of tobacco smoking or exposure to noxious agents presenting dyspnoea and/or chronic bronchitis [4].

By contrast, the definition of asthma is made on a pathological basis, and it is defined as a chronic airway inflammatory disease, characterized by infiltration of the airway mucosa by eosinophils, mast cells, and T lymphocytes, by sub-epithelial fibrosis, and almost constantly by intraluminal eosinophilia. Similarly to COPD, asthma is characterized by the presence of airflow limitation that, at difference with COPD, is completely reversible in most cases, either spontaneously or with pharmacological treatment [5]. Asthma clinically manifests itself with recurrent episodes of wheezing, breathlessness, chest tightness, and cough. Chronic airway inflammation is present in both COPD and asthma, even though the characteristics of the inflammatory process are markedly different in the two disease states [6,7].

Recently, it has been shown that airflow limitation may be progressive also in asthma, although to a lesser extent as compared to COPD, and thus it may shift from reversible to not fully reversible airflow limitation, as in COPD [8], making it difficult in some cases to distinguish the two disease states. Therefore, although the clinical, functional and inflammatory characteristics are usually markedly different in COPD and asthma, in clinical practice the differential diagnosis between these two respiratory conditions may become complex, particularly in the elderly or when there are overlapping features.

Indeed, it is "easy" to diagnose COPD in a 60-year-old life-long smoker with dyspnoea, chronic cough and sputum, and fixed airflow limitation. Similarly, it is quite easy to diagnose asthma in a young atopic non-smoking individual, with recurrent episodes of dyspnoea, wheezing or chest tightness, and variable and reversible airflow limitation. However, it might become difficult to differentiate between COPD and asthma in adults over 60 with confounding features, e.g., (i) smoking asthmatics or subjects with adult onset asthma, (ii) life-long non-smokers who present with fixed airflow limitation and no history of asthma, (iii) smokers with a clear history of COPD but also a significant degree of reversibility of the airflow limitation, (iv) non-smoking asthmatics with fixed airflow limitation, (v) subjects who report both diseases. In these cases the differential diagnosis between COPD and asthma may be difficult but nonetheless important, especially in terms of natural history [2] and response to pharmacological treatment [3].

Data from epidemiological studies have shown that there is a significant overlap between COPD and asthma. Asthma may be associated with reduced lung function in up to 20% of adults [9], and significant reversibility of airflow limitation to steroids have also been reported to occur in a significant proportion of subjects with COPD and no history of atopy or asthma [10]. Subjects who report both diseases have lower lung function and more respiratory symptoms than subjects with just one or the other [9]. Up to 12% of subjects with COPD are non-smokers (with a predominance of females) and there is evidence of increasing incidence with increasing age [11-13]. Over 20% of asthmatics are current smokers and the 22-43% of adult asthmatics are ex-smokers [14,15]. Current

asthmatic smokers, compared with never smokers, have more severe asthma symptoms, an accelerated decline in lung function, increase in hospitalization rates for asthma, and increased mortality following a near fatal asthma attack [16].

2. AIRWAY INFLAMMATION

Many studies have been conducted in the last 20 years on the airway pathology of COPD and asthma, mainly directed to understand the mechanisms of these two complex diseases, showing quite remarkable differences between the pathology of the two diseases [6,7,17,18].

In COPD the fixed airflow limitation is associated with an airway inflammatory profile consisting mainly of an increased number of T lymphocytes (predominantly $CD8^+$ lymphocytes) and macrophages in the bronchial mucosa, and neutrophils in the lumen [19,20]. By contrast, the variable airflow limitation in asthma is associated with a characteristic airway inflammation consisting of an increased number of T lymphocytes (predominantly $CD4^+$ lymphocytes) and eosinophils, and an increased thickness of the reticular layer of the epithelial basement membrane [21,22].

3. COPD

COPD is associated with inflammation of central and peripheral airways, lung parenchyma, and pulmonary vessels [6,17].

In the central airways, the characteristics of inflammation are: (i) an increased number of mononuclear cells, particularly macrophages and T lymphocytes of the $CD8^+$ type, associated in few cases with neutrophils, eosinophils and mast cells in the airway mucosa; (ii) increased number of neutrophils and, in few cases, of eosinophils in lavage fluid; (iii) infiltration of sub-mucosal glands by neutrophils; (iv) hyperplasia of goblet cells and enlarged mucous glands; (v) metaplasia of airway epithelium that is otherwise well preserved; (vi) no change of the structure of the lamina reticularis of the basement membrane. The contribution of these pathological abnormalities to airflow limitation and gas-exchange abnormalities still remains unclear. However, as airflow limitation progresses, the number of T-lymphocytes and macrophages increases in the sub-mucosa, and a particular subset of T-lymphocytes, the $CD8^+$ type, correlates significantly with the evolution of airflow limitation [23,24].

Peripheral airways show pathological abnormalities similar to those present in the central airways [23,24]. In addition, peripheral airways show increased intraluminal mucus and exudate, increased mass of smooth muscle, airway wall fibrosis, distortion, and obliteration, loss of alveolar attachments to the bronchiolar walls.

In the lung parenchyma, the typical pathological abnormalities are the presence of (*a*) pan-lobular emphysema (PLE) and centri-lobular emphysema (CLE) in various combination; (*b*) para-septal emphysema; and c) loss of vascular bed linked to emphysema.

Up to 20% of clearly defined COPD patients have a significant reversibility of airflow limitation to bronchodilators and/or glucocorticosteroids [10,25,26]. These patients seem to have the same pathologic abnormalities of COPD patients, but also some pathological features of asthma, namely a small but significant increase of eosinophils in bronchoalveolar lavage fluid, and a slight but significant increase of the thickness of the reticular layer of the basement membrane [10]. Moreover, in COPD with partial reversibility of airflow limitation, the bronchodilator response is associated with increased exhaled NO and sputum eosinophilia [27].

Epidemiologic studies show that 5-12% of subjects with fixed airflow limitation classified as COPD are nonsmokers and these subjects are predominantly female [12,13]. The inflammatory characteristics of these never-smoking patients presenting with a fixed airflow limitation are less known. Data from sputum analysis seem to show that there may be two distinct groups, one with increased and one with normal sputum eosinophil count [11].

4. ASTHMA

In asthma, most studies have included mild asthma, and have concentrated on biopsies from

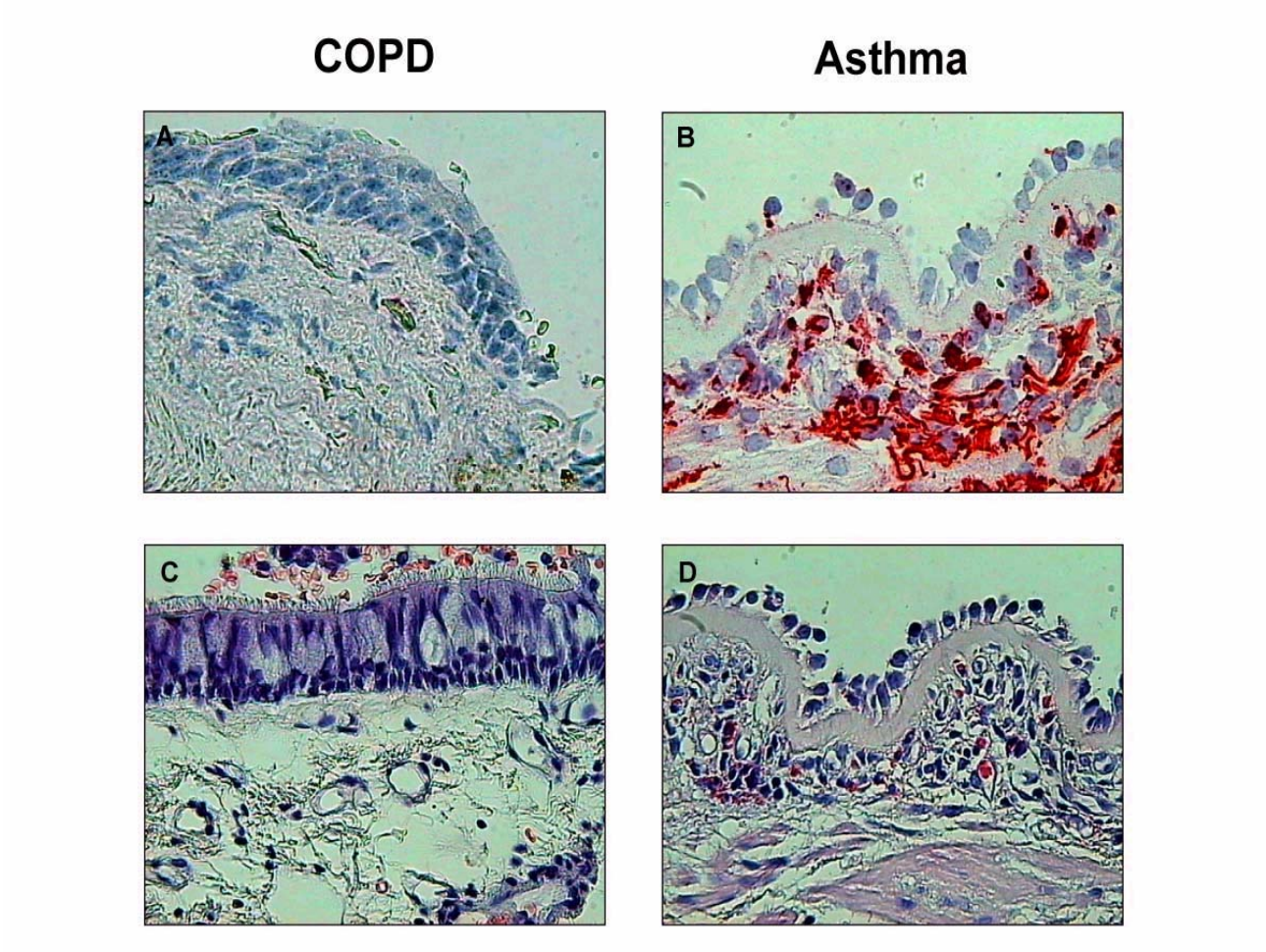

FIGURE 1. PANELS A AND B: PHOTOMICROGRAPHS SHOWING BRONCHIAL BIOPSY SPECIMENS IMMUNOSTAINED WITH ANTI–EG-2 (EOSINOPHIL CATIONIC PROTEIN) FROM A PATIENT WITH FIXED AIRFLOW OBSTRUCTION AND A HISTORY OF COPD (PANEL A) AND FROM A PATIENT WITH FIXED AIRFLOW OBSTRUCTION AND A HISTORY OF ASTHMA (PANEL B). The two patients had a similar degree of fixed airflow obstruction. In PANEL B, there is prominent eosinophilia beneath the destroyed epithelium that is not present in PANEL A. PANELS C AND D: Photomicrographs showing bronchial biopsy specimens stained with H&E from a patient with fixed airflow obstruction and a history of COPD (PANEL C) and from a patient with fixed airflow obstruction and a history of asthma (PANEL D). The two patients had a similar degree of fixed airflow obstruction. In PANEL D, there is a thicker reticular layer of the epithelial basement membrane compared with PANEL C [38].

central airways. These studies have consistently shown that asthma symptoms and airway hyperresponsiveness are associated with pathological abnormalities in central airways, whereas lung parenchyma is unchanged, at least in baseline conditions [21,28].

In the central airways of asthmatics, the typical pathological abnormalities are: (i) increased number of mononuclear cells, particularly T lymphocytes of the $CD4^+$ TH2 type, associated in most cases with eosinophils and mast cells in the airway mucosa and in the airway fluid, (ii) damaged airway epithelium, (iii) increased thickness of the lamina reticularis of the basement membrane [6,17]. The contribution of these pathological abnormalities to symptoms of asthma and airway hyperresponsiveness is unclear.

The peripheral airways of asthmatics have been examined only in one study, that showed substantially similar, although more severe, infiltration by T-cells and eosinophils [29].

TABLE 1. DIFFERENTIAL DIAGNOSIS BETWEEN ASTHMA, COPD AND ASTHMA WITH FIXED AIRFLOW LIMITATION (ADAPTED FROM [38]).

	ASTHMA	COPD	ASTHMA with fixed airflow limitation
Onset	At any time in life	In mid to late adult life	In mid to late adult life
Smoking	Usually non-smokers	Almost invariably smokers	Present/absent
Cough and sputum	Less common	Common (in "bronchitic" type)	Variable
Dyspnoea on effort	Variable	Predictable and progressive over months/years	Variable
Nocturnal symptoms	Relatively common	Uncommon	Uncommon
Airflow limitation	Increased diurnal variability	Normal diurnal variability	Variable
Response to bronchodilator	Good	Only in 15-25% of patients	Partially good
Airway hyper-responsiveness	In most patients, with or without airflow limitation	In most patients with airflow limitation	In most patients

Peripheral airways show: (i) increased intraluminal mucus and exudate, even of different composition with respect to the one observed in COPD, (ii) increased mass of smooth muscle, (iii) airway wall fibrosis, distortion, and obliteration, (iv) loss of alveolar attachments to the bronchiolar walls. These latter pathological abnormalities, however, have been described in the lungs of subjects who died of asthma, and it remains unknown whether they are present in the peripheral airways of living asthmatics.

The pathology of severe asthma, defined on the basis of chronic need of steroids (oral or inhaled at high doses) is less clear. Some studies have shown that the airway pathology of severe asthma is similar to the airway pathology to mild asthma, in particular involving eosinophils [30], even if the eosinophilic infiltrate looks more proximally distributed. By contrast, other studies have shown that severe asthma has a different pathology, with a predominance of neutrophils over eosinophils on bronchoalveolar lavage, endobronchial biopsies and transbronchial biopsies [31,32]. Interestingly, the thickness of the reticular layer of the basement membrane is similar in subjects with different athma severity [33]. A possible explanation for the differences in the inflammatory cells observed by some Authors between severe, steroid-dependent asthma and mild asthma is that the two forms of asthma have different pathologies, with a prominent neutrophilia in steroid-dependent asthma, and a prominent eosinophilia in mild asthma. An alternative explanation is that neutrophilia in steroid-dependent asthma may be the effect of steroid therapy itself, since glucocorticosteroids have been shown to inhibit neutrophil apoptosis [34]. Finally, it is possible that different inflammatory cell profiles in the airways may have been caused by different inflammatory stimuli, i.e. infectious stimuli in case of neutrophilia, and allergic stimuli in case of eosinophilia.

5. ASTHMA WITH FIXED AIRFLOW LIMITATION

The inflammatory characteristics of asthmatic patients who have developed fixed airflow limitation have been poorly investigated. Previous studies have compared airway inflammation in predefined patients with either asthma or COPD [35-37]. The limitation of those studies is that they compared young asthmatics with variable

TABLE 2. ADDITIONAL AND DISCRIMINATING TESTS IN THE DIFFERENTIAL DIAGNOSIS BETWEEN COPD AND ASTHMA WITH FIXED AIRFLOW LIMITATION (ADAPTED FROM [38]).

ADDITIONAL TEST	COPD	ASTHMA with fixed airflow limitation
Reversibility to steroids	Usually absent	Partially present
Residual volume	Usually increased	Normal or slightly increased
Diffusion capacity	Decreased	Normal or Slightly decreased
PaO_2	Usually decreased	Normal or Slightly decreased
HRCT emphysema score	Usually abnormal	Usually normal
DISCRIMINATING TESTS		
Medical history	(See Table 1)	(See Table 1)
Sputum and BAL eosinophilia	Absent	Present
Exhaled NO	Usually normal	Usually increased

airflow obstruction with older COPD patients with fixed airflow obstruction.

As mentioned above, the variable airflow limitation typical of asthma is associated with the characteristic airway inflammation consisting of an increased number of T lymphocytes (predominantly $CD4^+$) and eosinophils and an increased thickness of the reticular layer of the epithelial basement membrane [22], whereas the fixed airflow limitation in COPD is associated with an airway inflammatory profile consisting mainly of an increased number of T lymphocytes (predominantly $CD8^+$), macrophages, and neutrophils [19,20].

Based on this evidence, one could predict that in asthmatics developing fixed airflow limitation, airway inflammation would also change with the development of fixed airflow limitation and become similar to the airway inflammation of a COPD patient. If so, asthma could become COPD not only functionally but also pathologically. The recent investigation [38] of subjects with fixed airflow limitation with history of asthma or COPD, has shown that patients with a history of asthma have more eosinophils in peripheral blood, sputum, bronchoalveolar lavage fluid, and airway mucosa (FIG. 1) and they have fewer neutrophils in sputum and bronchoalveolar lavage fluid, compared with patients with a history of smoking-related COPD. Patients with a history of asthma have more bronchoalveolar lymphocytes and more CD4+ cells, a higher $CD4^+/CD8^+$ ratio, and a thicker reticular layer of the basement membrane in bronchial biopsy specimens. Finally, they produce a higher amount of exhaled NO. The percentage of sputum and bronchoalveolar lavage eosinophils and the NO level are good predictors of a history of asthma [38].

Therefore, the findings of this study suggest that asthmatic airway inflammation does not change with the development of fixed airflow limitation and does not become similar to the airway inflammation characteristic of COPD [7,38]. Thus, even when they develop fixed airflow limitation, patients with a history of asthma have the same airway inflammatory changes that are present in asthmatics with variable airflow limitation, indicating that asthma should be diagnosed and treated as asthma and not as COPD.

6. DIFFERENTIAL DIAGNOSIS

In most subjects the clinical presentation, and particularly the medical history provides the strongest diagnostic criteria to separate COPD from asthma (TABLE 1). Pulmonary function tests, and particularly spirometry, showing a nearly complete reversibility of airflow limitation in asthma and poorly reversible airflow limitation in COPD allows to confirm the diagnosis (TABLE 1).

Differential diagnosis between COPD and asthma becomes more difficult in elderly subjects when some of the features overlap, either smoking or atopy, and, more importantly, when the subject develops a poorly reversible or fixed airflow limitation that responds only partially to treatment. In these cases symptoms, lung function, and airway responsiveness may overlap, and thus may not provide solid information for the differential diagnosis. As the differential diagnosis mainly aims to provide better treatment, it is important in these cases to undertake an individual approach and to perform additional tests.

The comparison of patients with developed fixed airflow limitation induced by smoking-related COPD or asthma [38] has given some interesting tools in the differential diagnosis (TABLE 2). Reversibility of airflow limitation to steroids, residual volume, and arterial blood gases are different between fixed airflow limitation induced by smoking-related COPD or asthma. Subjects with fixed airflow limitation due to asthma have higher diffusing capacity and PaO_2 and lower residual volume and HRCT emphysema score, suggesting that lung parenchyma is less involved in asthma. By contrast, patients with fixed airflow obstruction due to COPD show lower diffusing capacity and PaO_2, and higher residual volume and HRCT emphysema score, suggesting that parenchymal destruction (i.e., emphysema) is present in COPD but not in asthma with fixed airflow limitation.

7. MANAGEMENT

Long-term treatment with inhaled corticosteroids represent the first-line treatment in persistent asthma (from mild to severe) [5], with the addition of a long-acting β_2-agonist in moderate to severe asthma. Thus, studies have demonstrated the efficacy of inhaled corticosteroids in improving lung function, decreasing airway hyperresponsiveness, reducing symptoms, reducing frequency and severity of exacerbations, and improving quality of life [5]. Most of patients with severe persistent asthma respond to corticosteroids in terms of clinical and functional improvement, although bronchoscopic studies showed that inflammation remains in severe symptomatic asthmatics which may be due to the severity of disease or other as yet undefined factors [31,39]. The effect of steroids on the decline of lung function associated with asthma [8] has not been examined, but indirect epidemiological evidence suggests that they reduce or even prevent it [2].

By contrast, in COPD, the first-line treatment is represented by bronchodilators, with the combination of inhaled corticosteroids indicated only in patients with severe and very severe COPD (FEV1<50% predicted) associated with frequent exacerbations [4,40]. Inhaled bronchodilators are recommended in the long-term treatment of COPD as it has been largely demonstrated that they improve symptoms, quality of life and exercise tolerance [4]. Some years ago, it was demonstrated that the addition of an inhaled corticosteroid, but not of an inhaled anticholinergic agent, to a maintenance β_2-agonist (terbutaline) treatment substantially reduced airway limitation in patients with a spectrum of obstructive airways disease, but particularly in those with a history of allergy and/or asthma [3].

Thus, interestingly, both in patients with moderate to severe asthma and in patients with severe to very severe COPD, the recommendation of current guidelines is to use a combination of long-acting bronchodilators and inhaled corticosteroids. However, the effect of this treatment is quite different in asthma and COPD. In fact, in asthma the combination of long-acting bronchodilators and inhaled corticosteroids induces a marked increase of lung function, reduction of symptoms and exacerbations, and of airway inflammation [41-43]. By contrast, the same treatment in COPD does not largely improve lung function or clinical parameters, nor it reduces the excessive decline of lung function over time [44-48]. However, it significantly reduces the incidence and severity of COPD exacerbations [49-52].

While the different effect of the bronchodilator component in the combination therapy may be related to the different structural causes of airflow limitation in asthma (more effective because of the more reversible "functional" airflow limitation, e.g., due mainly to smooth muscle contraction and edema) versus COPD (less effective because of the more “structural” and less reversible component, e.g. lung destruction and airway wall remodeling)

[38], the different effect of the steroid component of the combination is most likely due to the more effective anti-inflammatory effect of steroids in asthma [19,53] and the less effective anti-inflammatory effect of steroids in COPD [37,54].

As mentioned above, the differential diagnosis in patients with fixed airflow limitation may be important as the response to treatment is different, depending on whether fixed airflow limitation is due to asthma or COPD [3,38]. In fact, when fixed airflow limitation is developed in asthmatic subjects, airway inflammation still maintain the typical characteristics of asthma, being responsive to corticosteroids therapy and, thus, suggesting the use of corticosteroids in this particular group of patients, independently from the degree of airflow limitation [38].

8. CONCLUSIONS

In most cases, asthma and COPD present with distinct functional and pathological characteristics, that remain distinct even when asthma develop fixed airflow limitation. These differences may explain the better prognosis and the better response to steroids described in patients with fixed airflow limitation due to asthma compared with patients with fixed airflow limitation due to COPD. Therefore, in clinical practice, patients with fixed airflow limitation due to asthma should not be grouped under the general heading of COPD, and should be properly identified and treated.

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