

## Comparison of early and late asthmatic responses between patients with allergic rhinitis and mild asthma

M. Bonavia\*, E. Crimi\*\*, A. Quaglia\*, V. Brusasco\*\*

*Comparison of early and late asthmatic responses between patients with allergic rhinitis and mild asthma. M. Bonavia, E. Crimi, A. Quaglia, V. Brusasco. ©ERS Journals 1996.*

**ABSTRACT:** Allergic rhinitic subjects without symptoms of asthma show airway hyperresponsiveness, but to a lesser degree than asthmatics. As airway responsiveness is a determinant of the bronchial response to allergen, rhinitic subjects should also respond to allergen challenge, but to a lesser extent than asthmatics. However, studies have so far failed to show quantitative differences in allergen responses between patients with rhinitis and patients with asthma.

We studied 123 allergic subjects classified, on the basis of a scored symptom questionnaire, as follows: pure rhinitis without any symptom of asthma (Group 1, n=39), true asthmatics with or without rhinitis (Group 2, n=41), and subjects with borderline symptoms of asthma (Group 3, n=43). All subjects underwent both methacholine and allergen inhalation challenges, with pollen challenges performed out of season.

When the three groups were pooled, the asthma symptom score was directly correlated with the sensitivities both to methacholine and allergen, whilst both the sensitivity to allergen and the severity of late-phase response were correlated with the sensitivity to methacholine. The percentage of subjects with a positive early-phase asthmatic response to allergen was similar in Groups 1 and 2. Group 2 had higher sensitivities both to methacholine and to allergen than Group 1. A late-phase asthmatic response occurred more frequently in Group 2 than in Group 1, and this difference was due to a higher occurrence of late-phase response in subjects allergic to house dust mite in Group 2.

This study confirms that the bronchial response to allergen can be predicted, in rhinitic as well as in asthmatic allergic subjects, on the basis of airway responsiveness to methacholine. We conclude that the presence or the absence of asthma symptoms in allergic subjects may be related to a quantitatively different airway responsiveness to allergen.

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An increased airway responsiveness to pharmacological stimuli and a positive bronchospastic response to sensitizing stimuli are regarded as characteristics of allergic asthma [1]. In asthmatics, the degree of airway responsiveness to methacholine or histamine is, together with the degree of allergic sensitization, a predictor both of early [2] and late [3] bronchial responses to allergen inhalation. This, in turn, is predictive of the severity of symptoms upon natural exposure to allergen [4]. Subjects with allergic rhinitis who never experienced symptoms of asthma may also be hyperresponsive to pharmacological stimuli, but to a lesser degree than asthmatics [5–7]. If the data observed in asthmatics can be extrapolated to rhinitic subjects, it could be predicted that these also respond to inhalation of allergen, but to a lesser extent than asthmatics. However, studies in which asthmatic and rhinitic subjects were compared, failed to show quantitative differences in responsiveness to allergen between these two groups [5, 8, 9]. Thus, it is not clear why natural exposure to allergen does not also cause symptoms of asthma in subjects with allergic rhinitis. This inconsistency may result either from differences between experimental

and natural exposure to allergen or from the difficulty in categorizing rhinitics and asthmatics based on simple non-quantitative questions.

In this study, a quantitatively modified standardized questionnaire [10] was used to investigate whether atopic subjects with or without symptoms of asthma have different degrees of airway responsiveness to allergen or methacholine. It was found that, even if the occurrence of positive responses to allergen was similar in asthmatics and pure rhinitic subjects, the airway sensitivities to methacholine and allergen were higher in the former. This suggests that in atopic subjects the manifestation of asthma rely on a lower threshold of airway responsiveness to allergen.

### Methods

#### Subjects

We studied 123 atopic nonsmoking subjects, 70 males and 53 females, aged 16–58 yrs, with a history of rhinitis,

\*Divisione di Pneumologia Ospedale di Pietra Ligure, Savona, Italy. \*\*Cattedra di Fisiopatologia Respiratoria, DISM, Facoltà di Medicina e Chirurgia, Università di Genova, Genova, Italy.

Correspondence: V. Brusasco  
DISM, Facoltà di Medicina e Chirurgia  
Largo R. Benzi 10  
16132 Genova  
Italy

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or asthma [11], or both. To enter the study, subjects had to meet the following criteria: 1) to have a skin reaction to allergen equal to or greater than that elicited by a 10 mg·mL<sup>-1</sup> histamine; 2) to be in a stable clinical condition and to have a forced expiratory volume in one second (FEV<sub>1</sub>) within the normal range for age and sex [12]; 3) not to have suffered from asthmatic exacerbations or viral infections in the previous month; and 4) not to have been treated with inhaled steroids or cromones in the previous month. Short-acting bronchodilators had to be withdrawn 12 h before testing. No subject was taking theophylline, long-acting bronchodilators, or antihistamines. All patients were screened for allergy by skin-prick test (Lofarma, Milan, Italy) and radioallergosorbent test (RAST) (Pharmacia, Uppsala, Sweden) against the 12 most common local inhalant allergens (grass, mugwort, Parietaria, olive, Cupressus, birch, Dermatophagoides, Alternaria, Aspergillus, and cat, dog and horse dandruffs). Exclusion criteria were: 1) multiple allergic sensitization; 2) asymptomatic asthma in the previous 2 yrs; and 3) unstable lung function (see below).

At the first visit, the subjects completed a questionnaire regarding their respiratory symptoms in the previous 2 yrs. The questionnaire was an adaptation to atopic subjects of the questionnaire developed by the International Union against Tuberculosis and Lung Disease [10]. Questions were specifically addressed to those symptoms that have been shown to be good predictors of bronchial hyperresponsiveness [13], *i.e.* wheeze, waking at night with shortness of breath, and chest tightness upon exposure to allergen. In addition, questions on the occurrence of cough and sputum in the presence of allergens were included. Symptoms were scored 0 to 5 depending on their frequency, as follows: never=0; only once=1; once to three times per year=2; up to 12 times per year=3; more than monthly=4; more than weekly=5.

Subjects were assigned to three groups (table 1) depending on their cumulative asthma symptom score (CS). Group 1 comprised 39 pure rhinitic subjects (CS=0). Group 2 comprised 41 true asthmatic subjects with or without rhinitis (CS≥10 for any symptoms or ≥6 for wheeze, waking at night with shortness of breath, or chest tightness). Group 3 comprised 43 subjects with borderline symptoms of asthma with or without rhinitis (CS>0 but less than the above cut-off values).

The protocol was approved by the internal Ethics Committee and informed consent was obtained from all subjects.

Table 1. – Subject characteristics

Group	Age yrs	Sex M/F	FEV <sub>1</sub> % pred	CS	RAST TRA %
1 (pure rhinitis)	23 (21–28)	25/14	107±1.8	0 (0–0)	12±1
2 (true asthma)	26 (19–34)	24/17	107±1.9	11 (10–16)	13±0.8
3 (borderline asthma)	24 (18–29)	25/18	106±1.8	4 (3–6)	13±0.8

Values are presented as mean±SEM, or median and upper and lower quartiles in parenthesis. M: male; F: female; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: percentage of predicted value; RAST: radioallergosorbent test; CS: cumulative asthma symptom score; TRA: total radioactivity added.

### Bronchial challenges

Methacholine and allergen challenges were performed on two consecutive days, with the methacholine challenge always performed first. The spontaneous variability of airway calibre was monitored by measuring the FEV<sub>1</sub> hourly for 8 h after the resolution of the bronchospasm induced by methacholine. Subjects with daily variations of FEV<sub>1</sub> >10% of control value were not included in the study.

Allergen challenges with pollens were performed out of the pollen season. Methacholine and allergen were aerosolized by an ampoule-dosimeter device (MEFAR, Brescia, Italy) with identical ampoules being used throughout the study. The outputs were checked weekly by weighing the ampoules before and after inhalations. The dosimeter was set to deliver 5 µL of solution for 0.5 s at the beginning of each inspiration. The particle median mass diameter was 1.53–1.61 µm according to the manufacturing firm. Aerosols were inhaled during quiet tidal breathing.

The methacholine challenge was started from a dose of 10 µg, obtained by allowing one inhalations of a 0.2 % methacholine solution (Lofarma, Milan, Italy). Doubling increments of dose, *i.e.* 20, 40 and 80 µg, were obtained by allowing 2, 4, and 8 inhalations of the same solution. Further increments of dose, *i.e.* 150, 300 and 600 µg, were obtained by allowing 3, 6 and 12 inhalations of a 1% solution. Three measurements of FEV<sub>1</sub> were obtained within 5 min from the last inhalation of each methacholine dose by means of a turbine spirometer (Medical Graphics Co., St. Paul, MN, USA). The best of the three measurements was taken to construct the dose-response curves. The challenge was stopped when the FEV<sub>1</sub> decreased by 20% or more of postsaline control. When 600 µg of methacholine did not cause an FEV<sub>1</sub> decrease ≥20%, this dose was administered again to achieve a final cumulative dose of 1,790 µg. The cumulative provocative dose of methacholine causing a 20% fall in FEV<sub>1</sub> from control value (MChPD<sub>20</sub>) was calculated by interpolation of the dose-response curve. When a 20% FEV<sub>1</sub> decrease was not achieved, the PD<sub>20</sub> was arbitrarily considered to be 1,790 µg.

Allergen bronchial challenges were performed by using allergen extracts predosed in arbitrary units (au) by means of RAST inhibition technique against the corresponding in-house (Lofarma SpA, Milan, Italy) sera pools containing high titres of specific immunoglobulin (IgE). Lyophilized allergens were reconstituted by adding redistilled water to obtain 1,200 au·mL<sup>-1</sup>. Double decreasing solutions down to 18.75 au·mL<sup>-1</sup> were extemporaneously prepared by adding saline. Each allergen concentration was delivered for 0.5 s at the beginning of each inhalation, corresponding to an inhaled volume of 0.05 mL. Doses were increased with twofold increments from 0.93 to 120 au. The last dose was obtained with 20 inhalations of the 1,200 au·mL<sup>-1</sup> solution. The FEV<sub>1</sub> was measured in triplicate 15 min after each allergen dose until it fell by 20% or more of postsaline control. Thereafter, the FEV<sub>1</sub> was measured at 15, 30 and 45 min, and hourly for the following 8 h, in order to detect the occurrence of late-phase asthmatic response (LAR). Early-phase asthmatic response (EAR) and LAR were considered to be positive if FEV<sub>1</sub> decreased by ≥20% within 1 h from

the end of inhalation challenge and by  $\geq 15\%$  within the following 7 h, respectively. The cumulative provocative dose of allergen causing a 20% decrease of FEV<sub>1</sub> from control (AlgPD<sub>20</sub>) was calculated by interpolation of the dose-response curve. When a 20% FEV<sub>1</sub> decrease was not achieved, the cumulative AlgPD<sub>20</sub> was arbitrarily considered to be 239 au.

### Statistical analysis

PD<sub>20</sub>s were log transformed before statistical analysis and are presented as geometric mean (GM) with geometric standard error (GSEM) as a factor. All other results are presented as mean  $\pm$  SEM except age and CS, which are presented as median with lower and upper quartiles. Differences between groups were tested by analysis of variance (ANOVA) and unpaired Student's t-test. Chi-squared test was used to compare the frequencies of EAR and LAR. Pearson's ( $r_p$ ) or Spearman's ( $r_s$ ) correlation coefficients were calculated to assess the relationships between variables on pooled data. A p value of less than 0.05 was considered to be statistically significant.

## Results

There were no significant differences in anthropometric data, baseline lung function, or RAST between groups (table 1).

True asthmatic subjects (Group 2) had airway sensitivities both to methacholine and allergen significantly higher (*i.e.* lower MChPD<sub>20</sub> and AlgPD<sub>20</sub>) (fig. 1) than pure rhinitics ( $p < 0.0001$ ) (Group 1). This was also true when subjects sensitized to house dust mite or pollen were compared separately ( $p < 0.01$ ) (fig. 2). Within Group 1, the sensitivity to methacholine was significantly ( $p < 0.01$ )

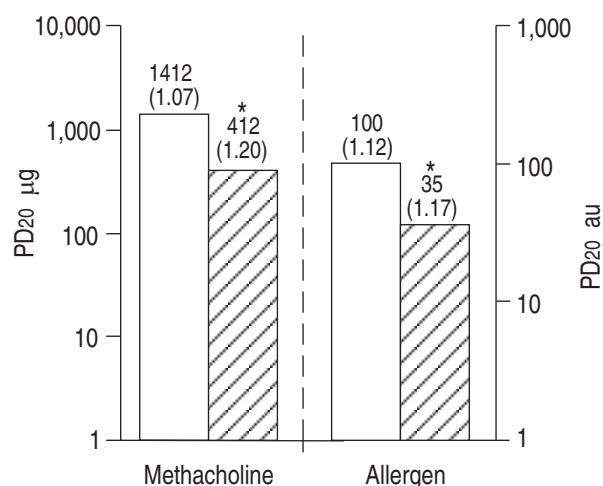


Fig. 1. — Airway sensitivities to methacholine and allergen in pure rhinitics (Group 1) and true asthmatic (Group 2) subjects. PD<sub>20</sub>: dose of methacholine or allergen causing a 20% decrease of forced expiratory volume in one second (FEV<sub>1</sub>); au: arbitrary units. □: Group 1; ▨: Group 2. Values indicate geometric mean with geometric standard error of the mean. \*: significantly ( $p < 0.0001$ ) different from Group 1.

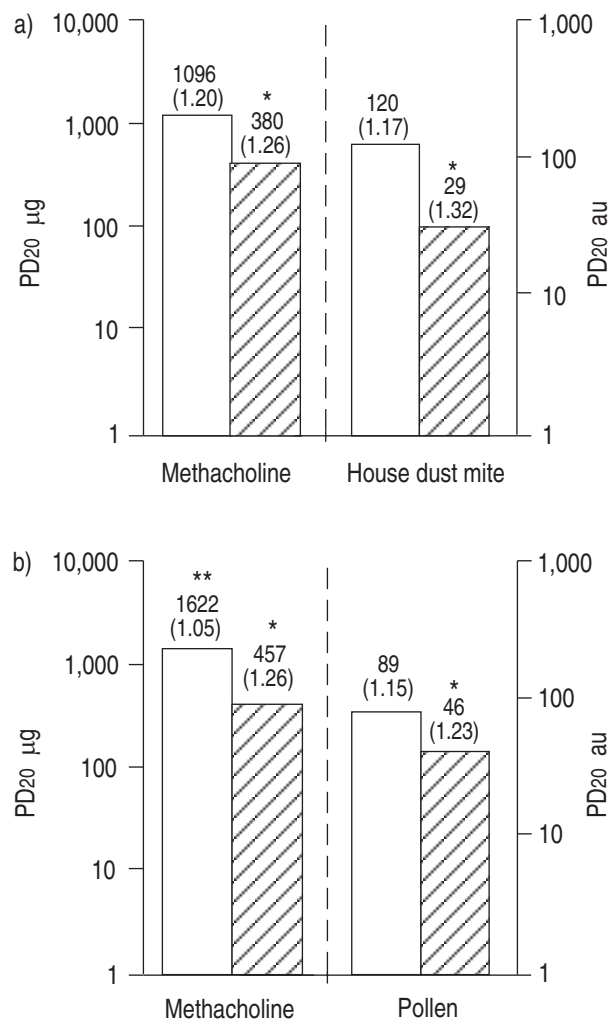


Fig. 2. — Airway sensitivities to methacholine and allergen in subjects allergic to: a) house dust mite; or b) pollen. □: Group 1 (pure rhinitic subjects); ▨: Group 2 (true asthmatic subjects). Values indicate geometric mean with geometric standard error of the mean in brackets. \*: significantly ( $p < 0.01$ ) different from Group 1. \*\*: significantly ( $p < 0.01$ ) different from rhinitics allergic to house dust mite

higher in subjects allergic to house dust mite than to pollen. Eight subjects of Group 1 and five of Group 2 had negative EAR. When these subjects were excluded from computation, the AlgPD<sub>20</sub>s were 87 au in Group 1 and 29 au in Group 2, a difference which was still statistically significant ( $p < 0.0001$ ). The frequency of LAR, but not of EAR, (fig. 3) was significantly ( $p < 0.01$ ) higher in Group 2 (positive to negative ratio 19/22) than in Group 1 (positive to negative ratio 6/33). This difference was due to a higher frequency of LAR in subjects sensitized to house dust mite of Group 2 (fig. 4).

In borderline subjects, MChPD<sub>20</sub> and AlgPD<sub>20</sub> were (GM) 1,045 µg and 89 au, respectively. The positive to negative ratios of EAR and LAR were 32/11 and 16/27, respectively. By including this group in the statistical analysis, significant correlations were found between MChPD<sub>20</sub> and either AlgPD<sub>20</sub> ( $r_p = 0.46$ ;  $p < 0.001$ ) or late FEV<sub>1</sub> fall ( $r_p = 0.2$ ,  $p < 0.05$ ). Furthermore, CS was significantly ( $p < 0.001$ ) correlated both with MChPD<sub>20</sub> ( $r_s = -0.53$ ) and AlgPD<sub>20</sub> ( $r_s = -0.39$ ).

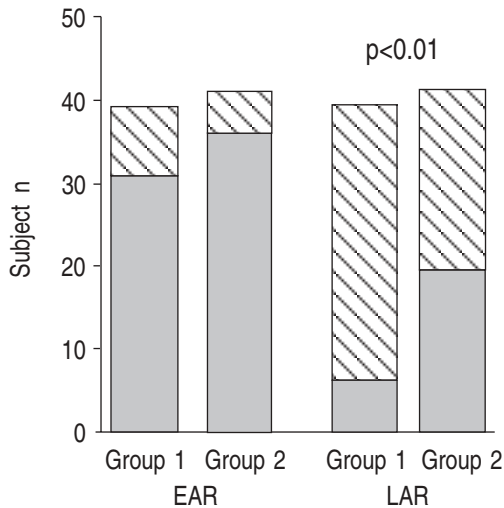


Fig. 3. — Distributions of subjects with negative or positive early (EAR) and late (LAR) phase asthmatic response to allergen. ■ : positive; ▨ : negative. Group 1: pure rhinitic subjects; Group 2: true asthmatics.

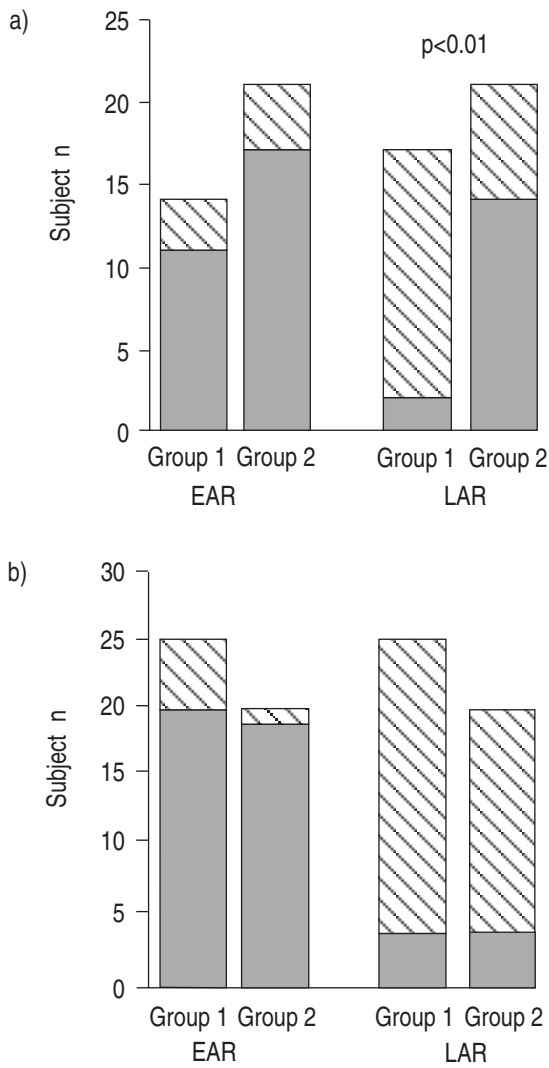


Fig. 4. — Distributions of subjects with negative or positive early (EAR) and late (LAR) phase asthmatic responses to allergen. to: a) house dust mite; or b) pollen. ■ : positive. ▨ : negative; Group 1: pure rhinitic subjects; Group 2: true asthmatic subjects.

**Discussion**

This study confirms that allergic subjects with symptoms of rhinitis only may have, like asthmatic subjects, a positive bronchial response to experimental exposure to allergen. The new findings are that subjects with asthma differ from subjects with pure rhinitis in having: 1) a higher airway sensitivity to allergen; and 2) a more frequent occurrence of LAR.

Asthma is characterized by reversible airway obstruction in response to different stimuli [1, 11,14]. In allergic asthmatics, the IgE-mediated response to allergen inhalation taking place in the airways is believed to be an important triggering factor for asthmatic symptoms. Moreover, baseline hyperresponsiveness to methacholine or histamine is a determinant of the intensity of airway response to allergen in asthmatics [3, 4]. It has been reported that rhinitic subjects are less responsive to pharmacologic stimuli than asthmatic subjects, but more than healthy subjects [5–9]. Therefore, rhinitic patients could also be expected to respond to allergen inhalation, but to a lesser extent than asthmatic subjects. Contrary to these predictions, a recent study [5] directly comparing asthmatic and rhinitic subjects with increased responsiveness to methacholine found no differences in bronchial responses to allergen. This similarity does not explain the difference in symptoms between these two groups.

At variance with MULLER *et al.* [5], we confirm that the degree of airway responsiveness to methacholine is also predictive of the bronchial response to allergen in subjects with rhinitis who have never suffered from asthmatic symptoms. Our conclusion is based on differences between groups that were distinctly separated by using a scored questionnaire and is supported by the results of regression analysis. In such a way, biases due to individuals with borderline symptoms were avoided. Crucial questions used to classify subjects were those shown to be specific for asthma and airway hyperresponsiveness [13]. Cough and sputum in the presence of allergens suggest involvement of the airways. However, they are not specific to airway hyperresponsiveness and asthma as they may be also observed in nonresponder subjects after exposure to allergen. For this reason, the symptom threshold to be defined a true asthmatic was increased from 6 to 10 if these symptoms were reported.

The use of bronchial allergen inhalation challenge as a model of allergic asthma may be criticized because the amount of allergen inhaled is abnormally high as compared to the amounts that may be inhaled during an equal period of natural exposure. However, the degree of airway responsiveness to allergen has been shown to be a good predictor of the severity of season asthmatic exacerbations [4]. The specificity of allergen challenge was assured by the absence of response in 12 healthy subjects challenged with several allergens and in 10 allergic asthmatics challenged with a nonsensitizing allergen (data not shown). This and the similarities of the inflammatory changes in the airways after experimental and natural exposure [15–17] makes us confident that allergen challenge can be used to quantify the severity of allergic asthma.

The positive response to allergen in pure rhinitics suggests that most of subjects sensitized to inhalant allergens are susceptible to developing a bronchospastic response,

provided they are exposed to sufficient amounts of allergen over a short time. This would imply that allergic asthmatics and allergic rhinitics belong to the same population, where the latter represent those subjects who have minimal risk of bronchoconstriction upon natural exposure to allergens. This is because of the low probability for rhinitic subjects to be naturally exposed to amounts of allergen sufficient to cause reduction of airway calibre and shortness of breath.

Bronchial challenge with pollen out of season caused a LAR in 15–25% of subjects, with no difference between pure rhinitic and true asthmatic subjects. By contrast, bronchial challenge with house dust mite, exposure to which is virtually perennial, caused LAR to occur more frequently in true asthmatic than in pure rhinitic subjects. These data are consistent with previous findings by STEVENS and VAN BEVER [18]. Surprisingly, however, these authors did not find any difference between rhinitic and asthmatic subjects regarding their sensitivity both to histamine and allergen. The higher frequency of LAR to house dust mite in asthmatic than in rhinitic subjects and the higher degree of sensitivity to methacholine in rhinitic subjects allergic to house dust mite than to pollen suggest that sensitization to house dust mite may increase the risk of developing chronic airway hyperresponsiveness and, perhaps, bronchial asthma.

In conclusion, the results of the present study indicate that subjects with allergic rhinitis without symptoms of asthma may respond to allergen inhalation, but to a lesser extent than asthmatic subjects. These data suggests that the difference in symptoms between allergic asthmatics and rhinitics relies on a quantitative difference in airway responsiveness to allergen. This implies that individuals with atopic asthma or pure rhinitis do not belong to different populations.

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