Acta Medica Okayama

Volume 46, *Issue* 5 1992 *Article* 9

OCTOBER 1992

Asthma classification by pathophysiology and IgE-mediated allergic reaction: new concepts for classification of asthma.

Yoshiro Tanizaki[*] Hikaru Kitani[†] Morihiro Okazaki[‡]

Takashi Mifune[**] Fumihiro Mitsunobu[††] Naoko Honke[‡‡]

Yasuharu Kusaura[§] Ikuro Kimura[¶]

[*]Okayama University,
[†]Okayama University,
[‡]Okayama University,
[**]Okayama University,
[††]Okayama University,
[‡‡]Okayama University,
[§]Okayama University,
[¶]Okayama University,

Asthma classification by pathophysiology and IgE-mediated allergic reaction: new concepts for classification of asthma.*

Yoshiro Tanizaki, Hikaru Kitani, Morihiro Okazaki, Takashi Mifune, Fumihiro Mitsunobu, Naoko Honke, Yasuharu Kusaura, and Ikuro Kimura

Abstract

Bronchial asthma was classified by the pathophysiology and by the mechanism of onset of the disease. Forty asthmatics who had serum IgE levels lower than 200 IU/ml were evaluated by two classification methods. 1. In asthma classified by a score based on clinical findings and examinations, the characteristics of the findings and examination results were compared among three asthma types, i.e., Ia. simple broncho-constriction type, Ib. bronchoconstriction+hypersecretion type, and II. bronchiolar obstruction type. Type Ib patients, in addition to manifesting hypersecretion, had a significantly higher proportion of eosinophils in the bronchoalveolar lavage (BAL) fluid compared to other asthma types. Significantly decreased values for ventilatory parameters and an increased proportion of BAL neutrophils were found in type II compared with other asthma types. 2. In a new classification by mechanism of onset, asthma was classified into three types according to the degree of participation of IgE-mediated reactions associated with specific IgE antibodies and serum levels of total IgE: asthma induced by definite IgE-mediated reaction (atopic asthma), possible IgE-mediated reactions (asthma), and asthma induced by non-IgE-mediated reaction (asthma syndrome).

KEYWORDS: asthma, asthma syndrome, classification by pathophysiology, classification by mechanism of onset

---

*PMID: 1442158 [PubMed - indexed for MEDLINE]

Acta Med Okayama 46 (5) 381-387 (1992)

Asthma Classification by Pathophysiology and IgE-Mediated Allergic Reaction: New Concepts for Classification of Asthma

Yoshiro Tanizaki, Hikaru Kitani, Morihiro Okazaki, Takashi Mifune, Fumihiro Mitsunobu, Naoko Honke, Yasuharu Kusaura and Ikuro Kimura[a]

Division of Medicine, Misasa Medical Branch, Okayama University Medical School, Misasa, Tottori 682-01, and [a]Second Department of Medicine, Okayama University Medical Scohool, Okayama 700, Japan

Bronchial asthma was classified by the pathophysiology and by the mechanism of onset of the disease. Forty asthmatics who had serum IgE levels lower than 200 IU/ml were evaluated by two classification methods. 1. In asthma classified by a score based on clinical findings and examinations, the characteristics of the findings and examination results were compared among three asthma types, *i.e.*, Ia. simple bronchoconstriction type, Ib. bronchoconstriction + hypersecretion type, and II. bronchiolar obstruction type. Type Ib patients, in addition to manifesting hypersecretion, had a singnificantly higher proportion of eosinophils in the bronchoalveolar lavage (BAL) fluid compared to other asthma types. Significantly decreased values for ventilatory parameters and an increased proportion of BAL neutrophils were found in type II compared with other asthma types. 2. In a new classification by mechanism of onset, asthma was classified into three types according to the degree of participation of IgE-mediated reactions associated with specific IgE antibodies and serum levels of total IgE: asthma induced by definite IgE-mediated reaction (atopic asthma), possible IgE-mediated reactions (asthma), and asthma induced by non-IgE-mediated reaction (asthma syndrome).

Key words : **asthma, asthma syndrome, classification by pathophysiology, classification by mechanism of onset**

Bronchial asthma is a syndrome, in which transient dyspnea and wheezing are exhibited. Although these are the predominant symptoms of asthma, the pathophosiological changes in asthmatic airways (which are related to the clinical symptoms) and the mechanism of onset vary because asthma is a syndrome.

* To whom correspondence should be addressed.

The pathophysiological changes that occur during asthma attacks are bronchoconstriction, swelling of the mucous membranes, and mucus hypersecretion, occasinoally accompanied by bronchiolar obstruction. We have classified asthma as being of three types according to pathophysiological airway changes related to clinical symptoms: Ia. simple bronchoconstriction type. Ib. bronchocostriction + hypersecretion type and

II. bronchiolar obstruction type (1-5). The mechanisms of onset of asthma have been extensively studied, and it is well known that the IgE-mediated allergic reaction participates in this mechanism (6-8). The presence of this reaction is, however, unclear in some adult asthma patients.

In the present study, we examined asthma classifications according to pathophysiological changes and according to the mechanism of onset. Here, we report the results and outline a new concept for the classification of bronchial asthma.

Subjects and Methods

To clarify the differences between the mechanism of the onset of asthma in atopic asthma with the IgE-mediated reaction (IgER) and that in non-atopic asthma without IgER, we examined 40 patients with asthma (23 females and 17 males). We selected patients with a low serum IgE level, between 0 and 200 IU/ml, for this study, because their maximum release and dose-response curves for histamine from basophils induced by anti-IgE were similar to those in healthy subjects (9,10). Their mean age was 49.7 years, with a range of 15-71 years, and the mean level of serum IgE was 93.2 ± 61.2 IU/ml ($\pm$ SD) (10-193 IU/ml). Of these 40 patients, 11 had specific IgE antibodies to inhalant allergens. Thirty-one healthy subjects (19 females and 12 males) were selected as controls. Their mean age was 55.5 years with a range of 15-72 years, and the mean level of serum IgE was 24.1 ± 20.7 IU/ml (0-89 IU/ml).

Asthma classification by clinical symptoms (clinical diagnosis) was performed according to previously described criteria (1-5), and summarized below:

Type Ia. Simple bronchoconstriction type: patients with symptoms such as wheezing and dyspnea, which are evoked predominantly by bronchoconstriction.

Type Ib. Bronchoconstriction + hypersecretion type: patients with symptoms due to hypersecretion (more than 100 ml/day of expectoration), in addition to bronchoconstriction.

Type II. Bronchiolar obstruction type: patients with symptoms evoked predominantly by bronchiolar obstruction.

In the present study, we carried out a new trial in an attempt to classify asthma by using a score (score diagnosis) calculated from clinical findings (expectoration per day, lung auscultation findings, *etc.*) and from examinations (ventilatory function test, cellular composition in bronchoalveolar lavage fluid (BALF) *etc.*) (11). Of the clinical findings and examinations, we selected the amount of expectoration per day, lung auscultation findings, $\%\dot{V}_{25}$ value, and proportion of BAL cells (neutrophils and eosinophils) for score diagnosis, since these findings and examination results showed the characteristics of each clinical asthma type. Suitable points were assigned to each of these findings and results: 5 points were given to the finding (expectoration more than 100 ml a day), only by which asthma type can be assessed, 4 points to findings and results, which are important for the classification, but require other conditions showing characteristics of each asthma type, and 1 point to findings and results suggesting to a certain extent characteristics of each asthma type. The criteria for score diagnosis are shown in Table 1.

Bronchoalveolar lavage (BAL) was performed in 34 of the 40 patients when they were free of symptoms. All patients in whom this examination was carried out were non-smokers. Informed consent for BAL procedure was obtained from all of the patients. The aspirates obtained by BAL examination were centrifuged at 1,200 rpm for 10 min at 4 °C, and the cell pellet was resuspended in Tris ACM (4,5). A differential cell count was performed in 500 cells excluding epithelial cells, on smear preparations

Table 1 Score for classification of asthma

Symtoms and laboratory findings	No of points
1. Expectoration more than 100ml a day	5
2. Expectoration between 50 and 99ml a day	4
3. Presence of sputum in several areas of the airways on auscultation	1
4. Day-long difficulty of expectoration	1
5. Transient bubbling rales in both lower lung fields on auscultation	4
6. Alveolar breath sounds in both lower lung fields markedly decreased or disappeared on auscultation	4
7. Value for $\%\dot{V}25$ less than 10%	4
8. Proportion of neutrophils in BALF more than 20%	4
9. Proportion of eosinophils in BALF more than 10 %	1

Classification: from 0 to 4 points; type Ia; from 5 to 11 points; type Ib; 12 points or more; type II.

stained with May Giemsa. The results were expressed as a percentage of total cells.

Ventilatory function was measured with a rolling-seal spirometer (Box Spiror 81, Chest Co) in all patients when they were at attack free stages.

Clinical findings were obtained by observing the patients' asthma attacks every day during their period of hospitalization. Amount of expectoration per day was recorded every day from 8.00 o'clock in the morning to 8.00 o'clock on the next morning. The result was expressed as a three-day mean when patients had asthma attacks with larger amounts of expectoration.

Specific IgE antibodies to allergens were assessed by radioallergosorbent test (RAST). The level of total IgE in sera was measured by radioimmunosorbent test (RIST).

Results

Characteristics of Asthma by Clinical Pathophysiology

Classification of asthma by score calculated from clinical findings and examinations. By clinical diagnosis, 32 of our 40 asthma patients were classified as type Ia, 2 as type Ib, and 6 as type II. By score diagnosis, in contrast, they were classified as follows; 26 type Ia patients, 8 type Ib, and 6 type II. The difference between the clinical and score diagnosis for the number of type Ia and Ib patients was due to the different criteria for the amount of expectoration per day in the two classification systems. Patients with expectoration from 50 to 99 ml/day were classified as type Ia by clinical diagnosis, and as type Ib by score diagnosis (Table 1).

Characteristics of asthma by score diagnosis. Table 2 shows the characteristics of asthma as classified by score diagnosis. In these asthma types, the mean age was highest in patients with type II, and there was no difference in mean age between types Ia and Ib. Serum IgE levels did not differ among the three types. Amount of expectoration per day was more increased in patients with types Ib and II than in those with type Ia. The mean score for asthma classification was highest in patients with type II and lowest in those with type Ia (Table 2).

Ventilatory function in asthma by score diagnosis. The values for %FVC, $FEV_{1.0}$%, $\%\dot{V}_{50}$ and $\%\dot{V}_{25}$ were significantly lower in

Table 2 Characteristics of asthma classified by score diagnosis

Asthma type	No of patients	Age (year)	Serum IgE (IU/ml)	Expect (ml/day)	Score	
					Mean	Range
Ia	26	49.0	88.7 ± 69.6	13.3 ± 7.0	0.46	0 − 1
Ib	8	47.8	88.0 ± 33.9	100.8 ± 77.8	6.25	5 − 7
II	6	54.8	119.5 ± 39.9	72.7 ± 72.0	16.50	13 − 22

Expect; expectoration

Table 3 Ventilatory function in asthma classified by score diagnosis

Asthma type	No of patients	Ventilatory function			
		%FVC	$FEV_{1.0}$%	$\%\dot{V}_{50}$	$\%\dot{V}_{25}$
Ia	26	$99.1^{a} \pm 18.6$	$72.2^{b} \pm 12.7$	$41.8^{c} \pm 21.2$	$31.8^{d} \pm 20.6$
Ib	8	94.5 ± 20.2	67.9 ± 12.5	34.7 ± 19.8	$26.1^{e} \pm 19.0$
II	6	$68.8^{a} \pm 25.2$	$53.0^{b} \pm 16.2$	$16.8^{c} \pm 9.8$	$12.4^{d,e} \pm 8.1$

a, *b* and *c*, $p < 0.01$; *d* and *e*, $p < 0.05$.

patients with type II than in type Ia patients. Patients with type Ib showed lower values for these parameters than type Ia patients, although the difference was not significant. The value for $\%\dot{V}_{25}$ was significantly lower in patients with type II than in those with type Ib. Only the value for $\%\dot{V}_{25}$ was significantly lower in patients with type II than in those with types Ia and Ib; this decrease in $\%\dot{V}_{25}$ is thus one of the characteristics of patients with type II (Table 3).

Cellular composition in the BALF of asthma patients by score diagnosis. Various blood cells migrate into the peripheral lung region; especially important in asthma are lymphocytes, neutrophils, and eosinophils. We examined the porportion of these in BALF and found that the proportion of lymphocytes in BALF did not significantly differ among the three asthma types. The proportion of neutrophils in BALF was significantly higher in patients with type II than in type Ia ($p < 0.001$) and type Ib ($p < 0.01$) (Table 4, Fig. 1). Amounts of eosinophils, which are closely related to allergic reactions, were significantly greater in the BALF of patients with type Ib than in those with type Ia ($p < 0.001$) and type II ($p < 0.05$). The increase in eosinophils in the BALF of type Ib patients did not differ markedly from the increase in those with types Ia and II (Table 4, Fig. 2).

Classification of Asthma by IgE-mediated Allergic reactions

Comparison of serum IgE levels in healthy and asthmatic subjects. The mean level of serum IgE in patients with asthma was significantly higher than the level in healthy subjects ($p < 0.001$). The asthmatic subjects were divided into two groups; patients with positive and negative RAST scores to allergens. The level of serum IgE in patients with positive

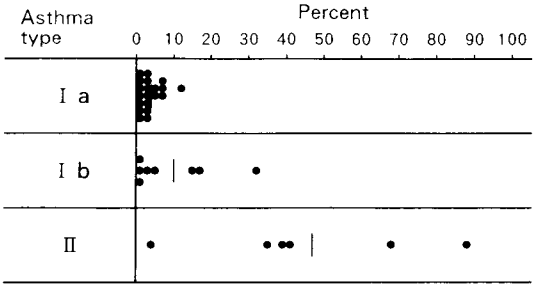

Fig. 1 Proportion of neutrophils in the bronchoalveolar lavage fluid (BALF) of asthma patients with serum IgE levels between 0 and 200 IU/ml in relation to asthma types classified by score diagnosis.

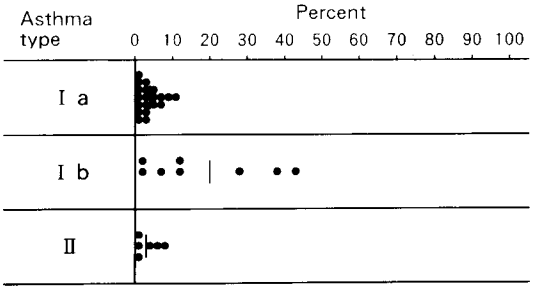

Fig. 2 Proportion of eosinophils in the bronchoalveolar lavage fluid (BALF) of asthma patients with serum IgE levels between 0 and 200 IU/ml in relation to asthma types classified by score diagnosis.

Table 4 Cellular composition of bronchoalveolar lavage fluid (BALF) in asthma patients classified by score diagnosis

Asthma type	No of patients	Cells in BALF (%)			
		Mac	Lym	Neut	Eos
Ia	20	$77.9^{a,b} \pm 13.5$	16.4 ± 11.3	$2.1^{c} \pm 2.8$	$2.8^{e} \pm 2.7$
Ib	8	$59.1^{b} \pm 18.0$	14.0 ± 5.5	$9.2^{d} \pm 10.8$	$15.0^{e,f} \pm 12.8$
II	6	$38.1^{a} \pm 21.7$	10.8 ± 10.2	$47.1^{c,d} \pm 28.4$	$3.1^{f} \pm 2.8$

Mac: macrophages; Lym; lymphocytes; Neut: neutrophils; Eos: eosinophils. *a*, *b* and *d*, $p < 0.01$; *c* and *e*, $p < 0.001$; *f*, $p < 0.05$.

RAST to allergens was significantly higher than the levels in those with negative RAST ($p < 0.02$) and the levels in healthy subjects ($p < 0.001$). There was also a significant difference between the serum IgE level of asthmatics with negative RAST and the level of healthy subjects ($p < 0.001$) (Table 5).

IgE-mediated allergic reaction in asthma. To evaluate the participation of the IgE-mediated reaction in the mechanism of onset of asthma, we compared serum IgE levels in two asthma groups, RAST positive and negative, and healthy subjects. Only one of the 11 (9%) patients with RAST positive to allergens showed a low serum IgE level, *i.e.*, under 50 IU/ml. In contrast, the level of serum IgE was lower than 50 IU/ml in 28 of the 31 (93.5%) healthy subjects. Thus, a serum IgE level of 50 IU/ml was evaluated as an upper limit indicating that the IgE-mediated reaction does not participate in the mechanism of onset of asthma. Levels of serum IgE lower than 50 IU/ml were observed in 12 of the 29 (41.4%) patients with serum IgE levels lower than 200 IU/ml and with negative RAST (Fig. 3).

Table 5 Comparison of serum IgE levels in asthmatic and healthy subjects

Subjects	RAST score	No of patients	Age, (years)	Serum IgE (IU/ml)
Asthmatic	Total	40	49.7	93.2 ± 61.2^{a}
	Positive	11	34.6	$132.4 \pm 56.8^{b,c}$
	Negative	29	55.3	$78.3 \pm 56.0^{b,d}$
Healthy	Total	31	55.5	$24.1 \pm 20.7^{a,b,c,d}$

a, *c* and *d*, $p < 0.001$; *b*, $p < 0.02$. RAST, radioallergosorbent test

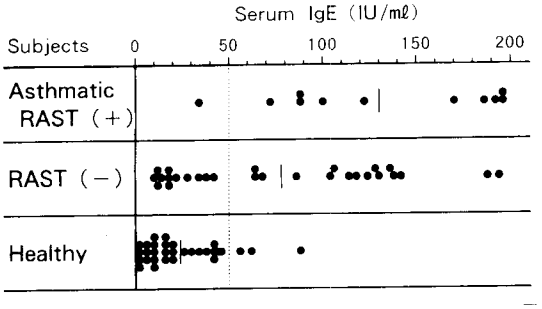

Fig. 3 Serum IgE levels in two asthma groups, radioallergosorbent test (RAST) positive and negative, and healthy subjects.

Discussion

Certain diseases have particular etiologies that lead to clinical symptoms. The concept of asthma as a disease is not clearly defined, and its mechanism of onset relative to its etiology and pathophysiology, which is evidenced by its symptoms, is very complex. To analyze the mechanism of onset and the pathophysiology of the disease, bronchial asthma should be classified according to the characteristics from these two points of view.

Our previous studies have shown that bronchial asthma can be classified by its clinical symptoms or pathophysiology into three asthma types as outlined above (1-5). In the present study, the classification by clinical symptoms (clinical diagnosis) was modulated by classification via a score calculated from clinical findings and examinations (score diagnosis) (11) to make asthma classification easier and objective more. For example, a difference between clinical and score diagnosis was observed in type Ia asthma with expectoration between 50 and 99 ml/day. These subjects were classified as type Ia by clinical diagnosis, but were evaluated as type Ib by score diagnosis, because their pathophysiology was similar to that of type Ib (11).

In type Ib asthma, we observed an increased proportion of eosinophils in BALF, and the increase was significantly higher than the increase in type Ia and II asthma when patients were selected from those with serum IgE levels lower than 200 IU/ml. Type Ib asthma in these subjects was characterized by an increased proportion of eosinophils in BALF in relation to hypersecretion. Decreased values of ventilatory parameters,

Table 6 Asthma classification by IgE-mediated allergic reaction

IgE-mediated reaction	Serum IgE (IU/ml)	Specific IgE antibodies	Asthma type	
			Coventional	New
Definite	0 − 50	+	Atopic	Atopic
	200 +	+ or −	−	Atopic
Possible	51 − 199	−	−	Asthma
No	0 − 50	−	Non-atopic	Asthma syndrome

especially the $\%\dot{V}_{25}$ value, and an increased proportion of neutrophils in BALF were clearly evident in patients with type II asthma. These characteristic examination results seemed to be related to the pathophysiology of asthma.

IgE-mediated allergic reactions have been shown to be related to the mechanism of onset of asthma (6-10,12,13). Burrows *et al.* found that serum IgE levels in asthmatic subjects were significantly higher than the levels in healthy subjects, suggesting the participation of IgE antibodies in the mechanism of onset of the disease in all their asthmatic subjects (14). Recent studies by Tollerud *et al.* support these findings (15). At present, we can classify bronchial asthma according to the presence or absence of the IgE-mediated allergic reaction. When so classifying, it is important to evaluate whether the IgE-mediated reaction participates in the mechanism of onset of the asthma. In the present study, to assess whether this was the case, we selected asthmatic subjects with serum IgE levels lower than 200 IU/ml for investigation (9,10).

The participation of the IgE-mediated reaction in the mechanism of onset of asthma has been confirmed by findings of specific IgE antibodies to allergens and increased levels of serum IgE, as described by Burrows *et al.* (14). It is clear that the IgE-mediated reaction is present in patients with specific IgE antibodies to allergens as shown by positive RAST score. In healthy subjects, in contrast, the IgE-mediated allergic reaction is not found. It is, however, unclear whether the IgE-mediated reaction participates in the mechanism of onset of asthma in subjects with low IgE levels under 200 IU/ml, and with negative RAST. To evaluate the presence or absence of the IgE-mediated reaction, we compared serum IgE levels in two asthmatic groups, RAST positive and negative subjects, and healthy subjects. We found the upper limit of the serum IgE level to be 50 IU/ml, which indicates that the IgE-mediated reaction is not implicated in the mechanism of onset of this disease. We speculate that the absence of the IgE-mediated reaction can be evaluated in the majority of asthmatic subjects whose serum IgE level is lower than 50 IU/ml and whose RAST score is negative.

We believe that bronchial asthma can be classified into three groups according to the degree of participation of the IgE-mediated reaction: asthma induced by definite IgE-mediated reaction, asthma induced by possible IgE-mediated reaction, and asthma induced by non-IgE-mediated reaction (Table 6). Definite IgE-mediated reaction is observed in patients with specific IgE antibodies to allergens, or in those with serum IgE levels more than 201 IU/ml. Possible IgE-mediated reaction is found in patients with negative RAST and serum IgE levels between 50 and 200 IU/ml, and non-IgE-mediated reaction is found in subjects with negative RAST and serum IgE levels lower than 50 IU/ml. We speculate that so-called atopic asthma is associated with definite IgE-mediated allergic reaction. Furthermore, we propose a novel classification of bronchial asthma, wherein, asthma that is induced by definite and possible IgE-

mediated reaction should be classified as asthma, and that asthma induced by non-IgE-mediated reaction should be classified as asthma syndrome (Table 6).

References

1. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Shiota Y, Tada S, Takahashi K and Kimura I: Classification of asthma based on clinical symptoms: Asthma type in relation to patient age and age at onset of disease. Acta Med Okayama (1984) **38**, 471-477.
2. Tanizaki Y, Komagoe H, Sudo M and Morinaga H: Clinical effect of spa therapy on steroid-dependent intractable asthma. Z Physiother (1985) **37**, 425-430.
3. Tanizaki Y: Improvement of ventilatory function by spa therapy in patients with bronchial athma. Acta Med Okayama (1986) **40**, 55-59.
4. Tanizaki Y, Sudo M, Kitani H, Kawauchi K, Mifune T, Takeyama H, Kohi F, Tada S, Takahashi K and Kimura I: Characteristic of cell components in bronchoalveolar lavage fluid (BALF) in patients with bronchial asthma classified by clinical symptoms. Jpn J Allergol (1990) **39**, 75-81 (in Japanese).
5. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Ochi K and Harada H: Cellular composition of fluid in the airways of patients with house dust sensitive asthma, classified by clinical symptoms. Intern Med (1992) **31**, 333-338.
6. Ishizaka T, Ishizaka K, Conrad DH and Froese A: A new concept of mechanisms of IgE-mediated histamine release. J Allergy Clin Immunol (1978) **64**, 320-330.
7. Ishizaka T: Analysis of triggering events in mast cells for immunoglobulin E-mediated histamine release. J Allergy Clin Immunol (1981) **67**, 90-96.
8. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kitani H, Goda Y, Tada S, Takahashi K and Kimura I: IgE-mediated histamine release from whole blood in atopic asthmatics. Jpn J Allergol (1983) **32**, 1079-1083.
9. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kitani H, Tada S, Takahashi K and Kimura I: Histamine release from whole blood induced by anti-IgE: Relationship to patient age, age at onset and serum IgE levels. Acta Med Okayama (1984) **38**, 275-281.
10. Tanizaki Y, Komagoe H, Morinaga H, Kitani H, Goda Y and Kimura I: Allergen- and anti-IgE-Induced histamine release from whole blood. Int Archs Allergy Appl Immunol (1984) **73**, 141-145.
11. Tanizaki Y, Kitani H, Okazaki M, Mifune T, Mitsunobu F, Kotoh N, Tada S, Takahashi K and Kimura I: Asthma classification by score calculated from clinical findings and examinations: Comparison between clinical and score diagnosis. Jpn J Allergol (1992) **41** (4), 15-22. (in Japanese).
12. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kitani H, Nakagawa S, Takahashi K and Kimura I: Reactivity of sensitized basophils, as expressed by histamine release. Jpn J Allergol (1984) **33**, 31-35.
13. Tanizaki Y, Sudo M, Kitani H, Kawauchi K, Mifune T, Takahashi K and Kimura I: Release of heparin-like substance and hstamine release from basophlic leucocytes separated by counterflow centrifugation elutriation. Jpn J Med (1990) **29**, 356-361.
14. Burrows B, Martinez FD, Halonen M, Barbee RA and Cline MG: Association of asthma with serum IgE levels and skin test reactivity to allergens. N Engl J Med (1989) **325**, 271-277.
15. Tollerud DJ, O'Connor GT, Sparrow D and Weiss ST: Asthma, hay fever, and phlegm production associated with distinct patterns of allergy skin testing, eosinophilia, and serum IgE levels: The normative aging study. Am Rev Respir Dis (1991) **144**, 716-781.

Received April 8, 1992; accepted May 29, 1992.