

The significance of mast cells in nasal smears from patients with food allergy

H. Shioda, M.D., and T. Mishima, M.D., Tokyo, Japan

Mast cells, as well as eosinophils, must be considered as significant cells in the allergic nasal response. There is a difference of interval between the appearance of the peak of eosinophils and that of mast cells in nasal secretions after allergen provocation. A definite increase of mast cells in nasal secretions suggests food allergy.

It is acknowledged that the presence of eosinophils in the nasal smear is important in the diagnosis of allergic disorders. Hansel¹ has emphasized this and has shown the relationship of the ratio of eosinophils to neutrophils in nasal smears in the diagnosis of allergic states.

However, to our knowledge, there have been few reports concerning the significance in allergic disorders of mast cells in nasal smears. Recently, Bryan and Bryan² have made a valuable contribution concerning the cytologic observations of nasal smears taken from patients with allergic problems. They reported that the significant cells in the allergic response were eosinophils, mast cells, and goblet cells. Furthermore, recent investigations have also shown that histamine and heparin are released by mast cells. Stimulated by these investigations, we have examined serial nasal smears from children with bronchial asthma and/or allergic dermatitis for mast cells and eosinophils. Smears were taken before, during, and after provocation with offending allergens. As a result of this study, we are suggesting that mast cells as well as eosinophils are significant cells in the allergic response, and that there is some correlation between mast cells and food allergy.

From the Pediatric Department, Sagamihara National Hospital, Sagamihara-shi, Kanagawa-Ken, and the Pediatric Department, Tokyo Zikei Medical College, Tokyo, Japan.

Received for publication June 21, 1965.

MATERIAL AND METHODS

Fourteen children with bronchial asthma and 3 children with allergic dermatitis and rhinitis probably of allergic cause had 236 nasal smears examined. The age of the patients ranged from 3 months to 12 years. Eleven were male and 6 female.

In all cases, the diagnosis of bronchial asthma and/or allergic dermatitis was confirmed by the history, physical examination, laboratory findings, and observation of the course of the problem. The offending allergens were elicited from the history, from skin tests (including Prausnitz-Küstner tests), by cytologic examination, and by challenge and response as noted in the nasal smears. The offending food allergens were ascertained by elimination and then evaluated by provocation tests. The offending inhalant allergens were confirmed by provocation tests with a vaponebulizer. All the elimination and provocation tests were done while the patients were under direct observation at Sagami-hara National Hospital. The individual cases are shown in Table I. The nasal smears were obtained by passing a straight cotton swab of suitable size along the floor of the nose and withdrawing it under the inferior turbinate with a twisting motion. The nasal secretions were rolled over two slides and immediately covered with 5 per cent Carbowax dissolved in 95 per cent ethyl alcohol. The slides were labeled and stained (Wright's stain) by the technique of Bryan. The time interval between smear and examination was long enough to obliterate memory of the particular patient's problem and name. The classification and gradation of the number of eosinophils, as described by Hansel, was modified for our use as noted in Table II. The mast cells on the nasal smears followed Bryan's numerical classification.

RESULTS

As shown in Fig. 1, in all specimens taken from children with definite food allergy (at least as one component of their allergies), the number of mast cells decreased significantly after the elimination of offending foods from the diet.

Following this observation, when any particular allergen was given to that specific-food-sensitive patient, the number of mast cells as well as eosinophils increased again, although the number varied in individual cases. However, there was a higher increase of eosinophils at the onset of induced asthmatic episodes, while the peak of mast cells was seen 24 to 36 hours after the provocation (Fig. 2).

Fig. 3 demonstrates the correlation found between the number of eosinophils and mast cells and the presence of positive responses to inhalant allergens by provocation in five children with bronchial asthma. There is an increase in the number of both kinds of cells in each case. There was a similar interval between the appearance of the maximal increase of eosinophils and that of mast cells. The number of eosinophils became less during the period of increased numbers of mast cells and tended to return to their preprovocation level as the number of mast cells decreased. It was suggested, however, that the increase in the number of mast cells seemed to be lower in this case when compared with the increase in mast cells produced by provocation with food allergens. As for eosino-

Table I. *List of patients*

<i>Patient</i>	<i>Age</i>	<i>Sex</i>	<i>Type of allergy</i>	<i>History</i>	<i>Skin tests</i>			<i>Offending and challenging allergens</i>
					<i>Scratch</i>	<i>Intra-dermal</i>	<i>Prausnitz-Küstner</i>	
H. N.	4 years	M	Asthma	+	+		+	Cow's milk
A. I.	3 months	M	Eczema	+	+		+	Cow's milk
A. N.	3 months	M	Eczema	+	+		+	Cow's milk
M. N.	1 year	M	Eczema	+	+		+	Egg white and cow's milk
I. I.	10 years	M	Asthma	+	+	+	+	Cow's milk and house dust
O. T.	5 years	M	Asthma	+	+	+		Egg white and house dust
O. A.	11 months	F	Asthma	+	+	+	+	Egg white, salmon, and house dust
T. M.	9 years	F	Asthma	+	+	+		Egg and house dust
K. H.	3 years	M	Asthma	+	+	+		Buckwheat and house dust
T. M.	4 years	M	Asthma	+	+	+		Egg and house dust
A. H.	6 years	F	Asthma	+	+	+		Potato and house dust
I. M.	12 years	M	Asthma	+	+	+		Egg, pork, and house dust
S. E.	10 years	F	Asthma	+	+	+		House dust and feather mixture
Y. T.	6 years	M	Asthma	+	+	+		House dust
K. Y.	8 years	F	Asthma	+	+	+		House dust and giant ragweed
H. M.	6 years	M	Asthma	+	+	+		House dust and short ragweed
K. K.	9 years	F	Asthma	+	+	+		House dust and short ragweed

Table II. *Gradation for the number of mast cells and eosinophils*

<i>Eosinophils</i>	
1+	A few scattered eosinophils or small clumps.
2+	A moderate number of eosinophils and larger clumps.
3+	Still larger clumps which, however, do not cover the entire field.
4+	Large clumps which cover the entire field.
<i>Mast cells</i>	
1+	15 to 25 cells in a whole slide.
2+	26 to 50 cells in a whole slide.
3+	51 to 100 cells in a whole slide.
4+	Over 101 cells in a whole slide.

In every grade, occasional neutrophils were seen in some areas of the slide.

phils, the opposite tendency was seen. In two infants with food allergies an increase of mast cells was noted after milk was given for three days, but no increase in eosinophils was observed (Patients A. I. and A. II., Table I).

In patients with more than one potential food allergen, the number of mast cells in nasal smears would not decrease unless all allergens were completely eliminated. The following case is a good example:

Case 1

O. A., an 11-month-old Japanese girl, was referred to the Sagami-hara National Hospital from another hospital in October, 1963, because of an annoying stridor. The family history,

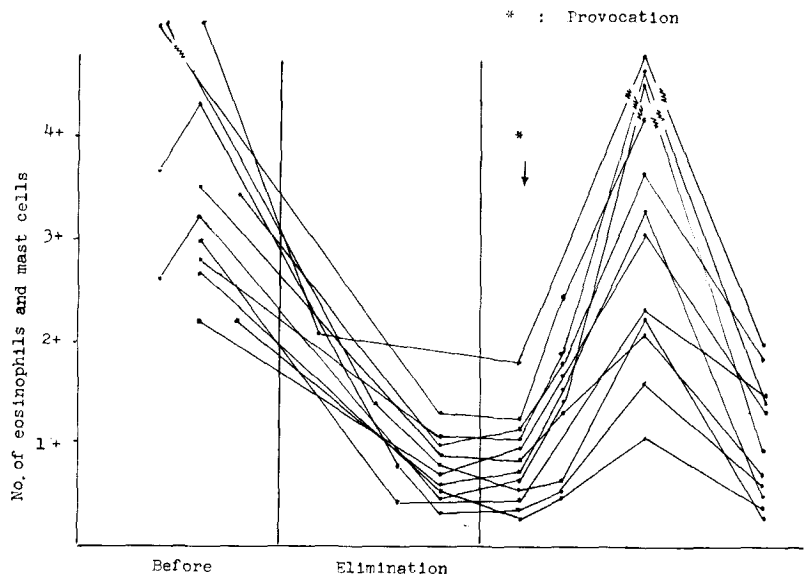


Fig. 1
The variation of mast cells after removal of offending food and before, during, and after provocation with the offending food allergens.

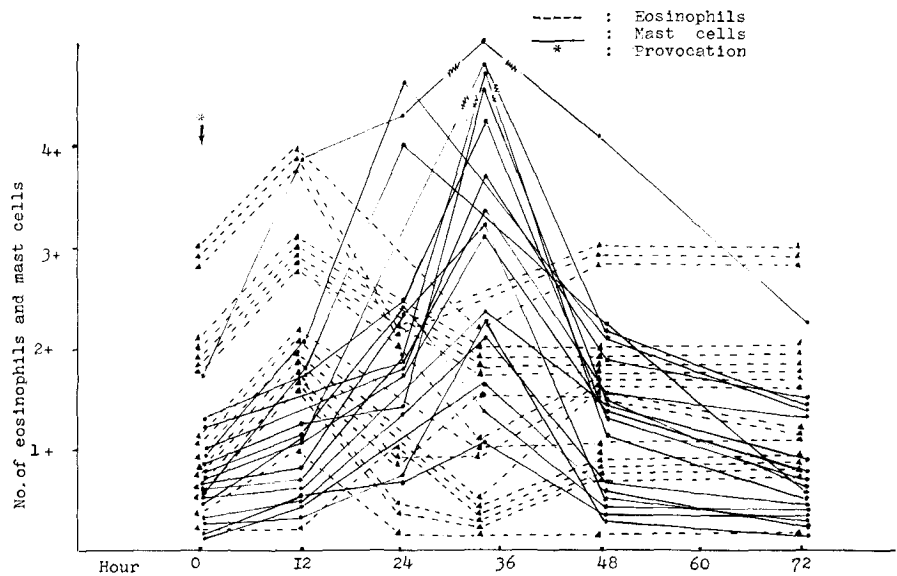


Fig. 2
The hourly variation of eosinophils and mast cells after provocation with food allergens.

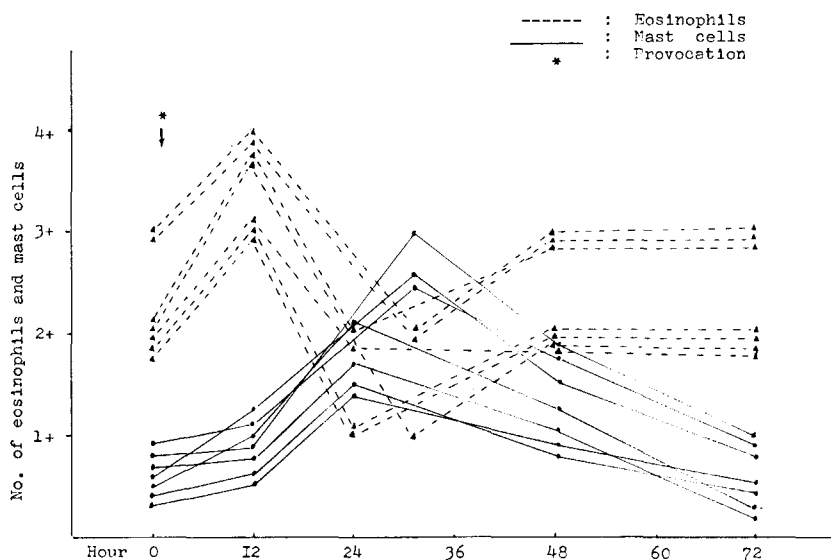


Fig. 3

The hourly variation of eosinophils and mast cells after provocation with inhalant allergens.

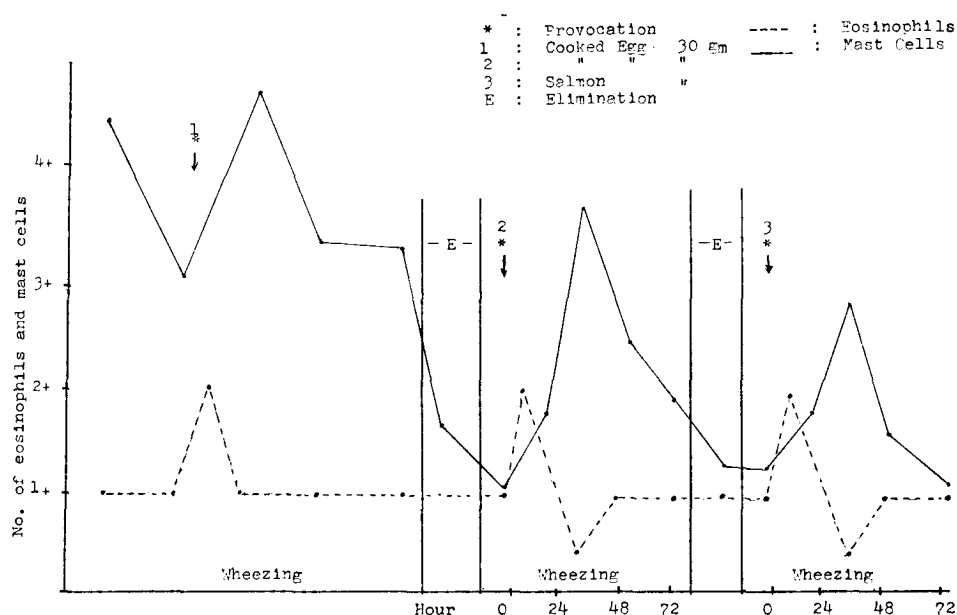
prenatal history, and postnatal history were noncontributory. The patient's weight at birth was 2,800 grams. The infant had been fed with breast and cow's milk.

At the age of 3 months she developed a generalized eczema which persisted for one-half year. At 7 months of age she had an episode of rhinorrhea, cough, and stridor which persisted for about a month. For a few days at the onset the infant had a fever.

At 9 months of age, on the night of Aug. 9, 1963, she developed an episode of dyspnea and fever (40° C.) and was admitted to a local hospital for approximately 20 days. During hospitalization she had no similar episode. However, soon after discharge from that hospital, the stridor reappeared and, thereafter, she continued to have episodes of rhinorrhea, cough, and stridor almost every day, requiring treatment at the ambulatory clinic of that hospital. In September, 1963, she was readmitted because of an increase of stridor and was treated without effect. Subsequently, she was transferred to our hospital for evaluation. At the time of admission, the patient was a malnourished female infant with inspiratory and expiratory stridor over the chest, and the nasal mucosa was boggy and covered with seropurulent discharge. As the result of repeated physical examinations and various laboratory tests, including skin tests, it was felt that the infant probably had food as well as inhalant sensitivities as the underlying cause. Scratch skin tests revealed markedly positive reactions for eggs and house dust, and weakly positive reactions for salmon and some other allergens. On the other hand, her nasal smears revealed 4+ mast cells as well as 1+ eosinophils on several occasions.

Considering these observations, she was treated by hyposensitization to house dust and elimination diets for egg, with the addition of symptomatic therapy. However, she continued to have moist rales. Weight gain was poor. The number of mast cells in the nasal smears did not decrease at all. Then the second scratch tests were performed, revealing almost identical positive reactions. However, it was found in the nurses' diet summary that canned salmon had been used as a substitute for egg and had been given almost every day. Surprisingly enough, the patient did show marked clinical improvement accompanied by negative mast cells in nasal smears, with avoidance of canned salmon. She gained 1.5 kilograms body weight during the first two weeks after this elimination.

Fig. 4 demonstrates the correlation between mast cells and eosinophils and the asthmatic episodes induced by offending food and inhalant allergen.

**Fig. 4**

Case 1, O. A., an 11-month-old girl with asthma.

The presence of many mast cells in nasal smears suggests that food allergy should be investigated or re-evaluated especially when the allergic symptoms do not improve with antiallergic treatment. The following case is an example:

Case 2

I. M., a Japanese boy 11 years and 10 months old was admitted to the hospital because of bronchial asthma. His mother had a history of urticaria, but otherwise there was no family history of allergy. In infancy, the patient had been breast fed. He had grown well without any allergic manifestations until 9 years of age. At that time, he began to have episodes of rhinorrhea, cough, and stridor lasting for a few days at a time. These episodes occurred four to five times a year. On Aug. 12, 1962, at 10 years of age, he developed an episode of cough and stridor at night without fever and had two similar episodes during the following three months. In March of 1963, he developed an episode of asthma and thereafter continued to have asthmatic episodes two to three times per month, increasing in frequency and severity in May. On Aug. 19, 1963, he was admitted to this hospital for evaluation. Soon after admission the asthmatic attack subsided and he had only an occasional mild asthmatic attack during two months' hospitalization. Further investigation of the patient's history at that time revealed that his family possessed 20 to 30 chickens, 5 to 6 pigs, one cow, and one cat. From the aforementioned history, feathers, cat hair, animal danders, house dust, some kinds of molds, and ragweed were suspected as possible offending allergens. However, skin tests revealed no definite positive reactions to food or to inhalant allergens. He was discharged on Oct. 17, 1963, without a particular offending allergen having been found. However, his family was advised to take care in cleaning the home. Empirically, a hyposensitization series with a commercial house dust extract was given, but the patient continued to have asthmatic attacks periodically. He was admitted to this hospital again on Aug. 31, 1964. At that time it was found accidentally that there were many mast cells and eosinophils in his nasal smears. As before, we could not determine any suspicious food allergen from his history or through skin tests. A strict diet was begun consisting of rice, salt, sugar, umeboshi (prunes), and

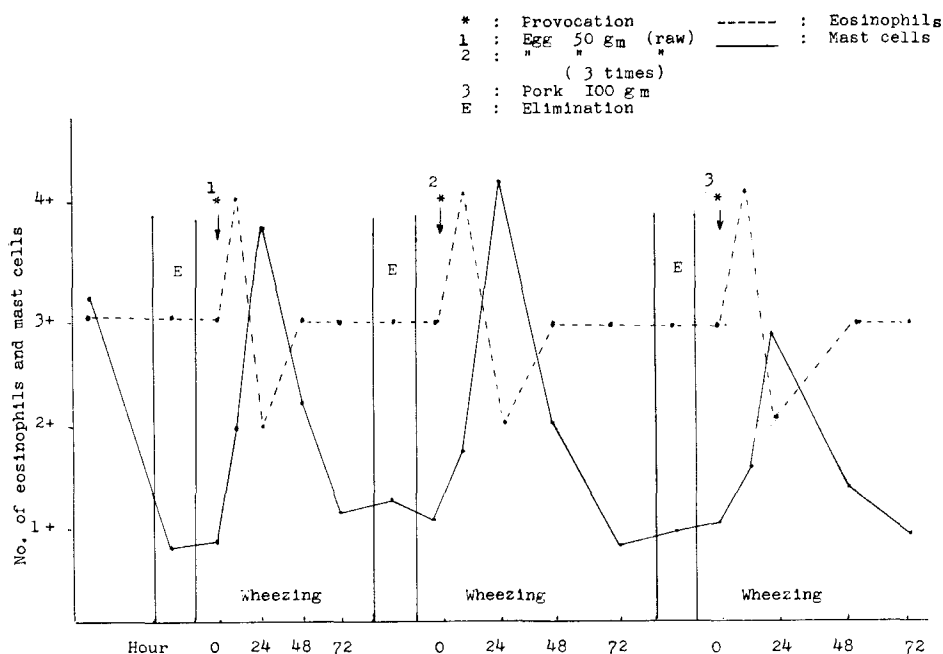


Fig. 5

Case 2, I. M., an 11-year-old boy with asthma.

multivitamins. During a 7 day period, his nasal smears were examined every day. During this period he had no asthmatic attacks, while the number of mast cells gradually decreased to 1+. Then, approximately 12 hours after the patient was given 50 Gm. of raw egg, an asthmatic attack of moderate severity occurred associated with serous nasal discharge. There were 4+ eosinophils and 1+ mast cells in the nasal smears taken at the time. In nasal smears taken about 24 hours after ingestion of the egg, 4+ mast cells and 2+ eosinophils were observed. Provocation tests with cow's milk and peanuts were attempted with no clinical symptoms and no particular increase of mast cells or eosinophils in the nasal smears. A second provocation with egg again revealed similar positive results. Fig. 5 shows the nasal cytologic responses. About 8 days after an induced asthmatic episode, a provocation with a pork steak was performed which also induced an asthmatic attack a few hours later. Similar responses were observed in the nasal cytology study. As a result of the positive response to egg intake, it was found, retrospectively, that this boy had often eaten Japanese rice with raw eggs and that he liked peanuts and pork products. House dust extract from his home environment is now being prepared and is to be used for skin tests and therapy, if necessary.

DISCUSSION

Recent investigation has shown that the granules of mast cells contain histamine, heparin, and so forth, which have been considered as chemical mediators of the allergic processes. It is very important to elucidate a more exact correlation between mast cells and allergic responses. To our knowledge, in 1959, Bryan and Bryan² suggested for the first time that the mast cell is prominent and of significance in the allergic nasal response. They mentioned the correlation of eosinophils with inhalant allergy and of mast cells with food allergy. In order to explore these observations, we have examined the mast cells and eosinophils

in nasal smears serially taken from children with allergic disorders whose allergens were ascertained by provocation tests. It was observed that the numbers of both eosinophils and mast cells in nasal smears increased significantly when clinical allergic manifestations were induced by challenge with the particular inhalant or food allergen. However, a different interval was found between the peak appearance of eosinophils and that of mast cells. The peak in mast cells was seen approximately 25 hours after the provocation and, subsequently, the number decreased in a relatively short period. One may miss the significance of mast cells if this fact is not kept in mind. This fact may explain Bryan's³ observation that a patient who is known to have a food allergy occasionally has shown only eosinophils and at other times only mast cells. We could not determine as specifically as Bryan the correlation of eosinophils with inhalant allergen and of mast cells with food allergen. However, first, there was seen a decrease in the number of mast cells in nasal smears after elimination and an increase by provocation with the offending food allergens. Second, there was no change in the number of mast cells in nasal smears by the giving of nonoffensive food allergen, as clearly shown by the representative Case 2. These facts suggest that at least there is some intimate correlation between mast cells and food allergen.

It needs to be emphasized that there was no definite decrease of mast cells in nasal smears so long as the offending food allergen remained in the diet causing clinical symptoms. Recently, Johnson⁴ has found no definite correlation between the presence of mast cells in the nasal smears and positive scratch skin tests or histories suggesting food allergy. However, his criteria for a significant number of mast cells were different from ours. The greatest number of mast cells in the nasal smears from his patients was described only as more than ten. In addition, the diagnosis of food allergy was not necessarily made in his patients with the use of elimination and provocation tests.

Even before this significance is completely elucidated, mast cells can serve as one of the cytologic indicators of the allergic response.

We wish to express our appreciation to Dr. Donald L. Thurston, Dr. William T. K. Bryan, and Marian P. Bryan for their valuable assistance.

REFERENCES

1. Hansel, French K.: *Clinical Allergy*, St. Louis, 1953, The C. V. Mosby Company, p. 413.
2. Bryan, William T. K., and Bryan, Marian P.: Cytologic Diagnosis in Otolaryngology, *Trans. Am. Acad. Ophth. & Otolaryng.* **63**: 597, 1959.
3. Bryan, William T. K., and Bryan, Marian P.: Significance of Mast Cells in Nasal Secretions, *Trans. Am. Acad. Ophth. & Otolaryng.* **63**: 613, 1959.
4. Johnson, Kenneth J.: Mast Cells and Eosinophils in Food and Inhalant Allergy, *Ann. Allergy*, **20**: 657, 1962.