

A STUDY OF FACTORS CONTRIBUTING TO BAKERS' ALLERGY SYMPTOMS

Yasuhiro Matsumura, Tomoyuki Niitsuma and Hisao Ito
The Third Department of Internal Medicine, Tokyo Medical College

It has been known for many years that bakers, who work in an atmosphere filled with wheat flour and other grain products, often suffer from bronchial asthma and other allergy symptoms. We examined 36 cooks (males: 33, females: 3, average age: 29.1 years) exposed to wheat products while baking bread or making confectioneries in a hotel. Their clinical symptoms were investigated, and peripheral blood eosinophils, serum IgE, wheat flour specific IgE, IgG1, IgG4, and antibodies to α -amylase and papain were measured. Clinical symptoms were present in some cases, the most common being rhinitis (13), itching and skin eruptions (8), ocular symptoms, including tearing, itching and conjunctival injection (8), and respiratory symptoms, including cough and sputum production (8). Wheat flour specific RAST was positive in 44.4% of cases. Peripheral eosinophils and wheat flour specific IgG1 levels were increased in those with positive RAST scores. Total IgE level and wheat flour specific IgG4 also seemed to be increased in those with positive RAST scores. Wheat flour specific IgG1 and IgG4 seemed to correlate positively with wheat flour specific IgE. The exposure duration correlated with neither total IgE nor wheat flour specific IgE. In those who were wheat flour RAST positive, wheat flour specific IgG1 levels correlated negatively with exposure duration. In RAST negative cases, however, there was no correlation. Similarly, there seemed to be a tendency for wheat flour specific IgG4 levels and exposure duration to correlate negatively in RAST positive cases. The subjects of this study initially worked in poorly ventilated areas. There was a tendency for IgE and IgG1 levels to decrease after the installation of an air purifier and the introduction of other protective measures. We did not however, find a clear relation between IgG subclass levels and clinical symptoms. Therefore, the IgG subclass can serve only as an index of allergen exposure. Among the wheat flour RAST positive cases, there was a tendency to be mite, barley and rye RAST positive as well. This suggests that atopic mechanisms contribute to wheat flour sensitization. The RAST scores for baking additives, such as α -amylase and papain, were also determined in 13 cases. Two cases (15.4%) were both α -amylase and papain positive. These results indicate that bakers' allergic symptoms do not result from wheat flour allergy alone, but rather are a composite of allergies to various materials.

Key words: α -amylase — papain — wheat flour specific IgE — wheat flour specific IgG1 — wheat flour specific IgG4

INTRODUCTION

It has long been recognized that bakers, who work in an atmosphere filled with wheat flour and other grain products, frequently suffer from bron-

chial asthma and other allergic disorders. Baker's asthma had become well known since Ramazzini's first report in 1700 and Baago's systematic investigation in 1933¹⁾. Many studies concerning baker's asthma have been published in European countries and the United States²⁾³⁾⁴⁾. Though approximately 70 occupational allergies have been reported in Japan, few investigations have dealt with baker's asthma⁵⁾⁶⁾. Recently, because of eating habit changes in Japan, cooks and bakers now handle large quantities of wheat flour. Furthermore, they usually work in insufficiently venti-

Received: November 4, 1993

Accepted: March 15, 1994

Abbreviations: ELISA enzyme-linked immunosorbent assay; RAST radioallergosorbent test; RIST radioimmunosorbent test

Table 1 Worker's profile

No.	Age	Sex	Period of exposure (year)	Nasal symptom	Cutaneous symptom	Conjunctival symptom	Respiratory symptom	Past history	Peripheral Eosinophile (/mm ³)	IgE	Wheat RAST score	Wheat IgG1 (U/ml)	Wheat IgG4 (U/ml)	Scratch test	α -Amylase RAST score	Papain RAST score
1	36	m	10	+	-	-	+	asthma	69	380	4	0.255	7.3	+	0	1
2	28	m	4	+	-	-	+		348	670	4	1.237	>8	+	0	1
3	24	m	4	+	-	-	+		592	200	4					
4	23	m	4	+	+	+	-		255	160	3	0.377	1.8	+	0	0
5	25	m	4.5	+	+	+	+		498	200	3	0.663	3			
6	25	m	5	-	-	-	-		446	410	3	0.23	2.3	+	0	0
7	22	m	3.5	+	+	-	+		163	100	3		1.9	+		
8	29	m	12	+	+	+	+		561	56	3	0.135	0.4	+	0	0
9	23	m	5	+	-	+	-		288	280	3		5.7	+	0	0
10	30	m	12	+	+	+	+		238	2800	3	0.294	0.7			
11	24	m	4.5	-	-	-	-		111	140	2	0.211	>8			
12	23	m	4	+	+	+	-		540	8000	2	1.042	>8	-	2	2
13	21	f	0.67	-	-	-	-	rhinitis	80	770	2	0.258	>8			
14	22	m	2.16	-	-	-	-		60	30	2	2.156	>8			
15	40	m	16	+	-	-	-		350	85	2	0.045	1.7	+	0	0
16	33	m	12	-	-	-	-		502	2100	2	0.272	1.2			
17	20	m	0.16	-	-	-	-	atopic dermatitis, rhinitis	174		1	0	3.8	-	2	2
18	22	m	3	-	-	-	-	rhinitis	168	1900	1	0.21	2.8			
19	23	m	4	-	-	-	-	rhinitis	41	94	1	1.096	2.7	-		
20	39	m	18	-	-	-	-		62	11	0	0.242	1.2			
21	30	m	3	-	-	-	-		216	59	0	0.45	1.3	-	0	0
22	30	m	9	+	-	-	-		162	130	0	0.017	0.3			
23	28	f	10	-	-	+	-		150	15	0	0.072	<0.3			
24	37	m	15	+	-	+	-		39	49	0	0.108	0.8			
25	47	m	10	-	-	-	-		204	88	0	0.294	<0.3			
26	25	m	4	-	-	-	-		146	96	0	0.207	<0.3	-		
27	58	m	30	-	-	-	-		59	270	0	0.245	0.7			
28	35	m	18	-	-	-	-		365	120	0	0.205	1.3			
29	24	m	5.67	-	-	-	-		836	110	0	0.071	0.6			
30	36	m	9	-	-	-	-		144	32	0	0.26	6.2			
31	29	m	7	-	-	-	-		85	43	0	0.008	<0.3			
32	29	f	11	-	-	-	+		184	140	0	0.289	<0.3			
33	28	m	0.08	-	-	-	-		142	<10	0	0.108	<0.3			
34	29	m	10	-	+	-	-		25	<10	0	0.552	2.7			
35	33	m	15	-	+	-	-		99	17	0	0.364	0.6			
36	19	m	0.67	-	-	-	-		264	47	0	0.023	0.4			
	Mean		7.49	Total 13	Total 8	Total 8	Total 8									
	29.1															

lated areas.

Wheat flour has been identified as a major allergen, and contains allergenic substances such as gluten, water insoluble agents, and albumin⁷⁾. Pfeil et al.⁸⁾ reported that water soluble wheat flour allergens were identifiable components with molecular weights of 47, 17 and 15 kD. In addition, other agents which are found together with wheat flour, such as house dust, mites, fungi or grain weevils, are presumed to causes of allergy⁹⁾. Furthermore, Flindt and Baur et al pointed out that baking additives, such as α -amylase and papain, have also been identified as allergens¹⁰⁾⁻¹²⁾. As so-called baker's asthma cannot be explained by a single allergen, we studied this disease from the aspects of sensitization to wheat flour and other agents, as well as contributing factors and clinical features.

MATERIALS AND METHODS

The study population consisted of 36 cooks (males: 33, females: 3, 19-58 year-old, average age: 29.1 years, SD: 8.1) who handled wheat flour when baking bread or making confectioneries in a hotel (Table 1). Data concerning occupational exposure duration, symptoms and any personal history of asthma or other allergic disorders were obtained by questionnaire. After investigating each individual's allergy history, immunologic and allergic status was evaluated with reference to peripheral blood eosinophils (/mm³), serum IgE (U/ml), wheat flour specific IgG (PRU), wheat flour specific IgG1 (U/ml), wheat flour specific IgG4 (U/ml), and antibodies to α -amylase (PRU/ml, RAST score) and papain (PRU/ml, RAST score). The total amount of IgE in serum was determined by the RIST (radioimmunosorbent test [Kabi Pharmacia, Uppsala, Sweden]) method. Allergen specific antibodies against wheat flour, mites, house dust, barley and rye were detected by the RAST (radioallergosorbent test [Kabi Pharmacia]) method. Positive findings were categorized as class 0 (below 0.34 PRU); class 1 (0.35-0.69); class 2 (0.70-3.49); class 3 (3.50-17.4); class 4 (above 17.5). Scratch tests for wheat flour (Torii, Tokyo, Japan) were performed in some cases. Wheat flour-specific IgG1 was measured by

an enzyme-linked immunosorbent assay (ELISA) with dried wheat powder (Torii) and anti-human IgG1 monoclonal antibody (Zymed Laboratories Inc. San Francisco, USA). Wheat flour-specific IgG4 was determined by ELISA with dried extracted wheat powder (Torii) and peroxidase labeled anti-human IgG4 monoclonal antibody (Yamasa Soy Sauce, Chiba, Japan). Eosinophils, IgE, wheat flour RAST, wheat flour IgG1 and wheat flour IgG4 were measured six months after the introduction of protective measures such as wearing a mask (3M, 8710 for dust) and installation of an air purifier (Hitachi, industrial, RG500 max velocity 50 m³/min, max vacuum degree 300 mmHg₂O).

Detection of antibodies to α -amylase and papain was performed by the RAST RIA method employing and Allergo-Disc anti- α -amylase (K87, Kabi Pharmacia), and anti-papain RAST discs (RK201, Kabi Pharmacia).

RESULTS

In the present study, clinical symptoms were present in some cases, the most common being rhinitis (13; 36.1%), followed by itching and skin eruptions (8; 22.2%). Ocular symptoms included tearing, itching and conjunctival injection (8; 22.2%). Respiratory symptoms consisted of cough and sputum production, (8; 22.2%) (Fig. 1). There was a tendency for nasal symptoms to appear somewhat earlier than other symptoms¹³⁾ but incidence decreased as the duration of exposure increased. There was no significant relationship between other symptoms and exposure duration.

Wheat flour specific RAST was positive (RAST score above 2) in 44% of cases. There was a significant relation between wheat flour specific

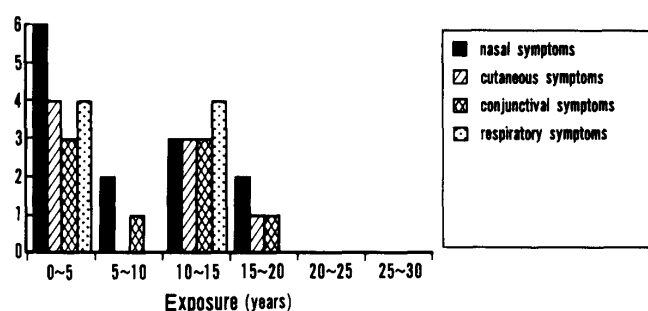


Fig. 1. Symptoms and exposure duration.

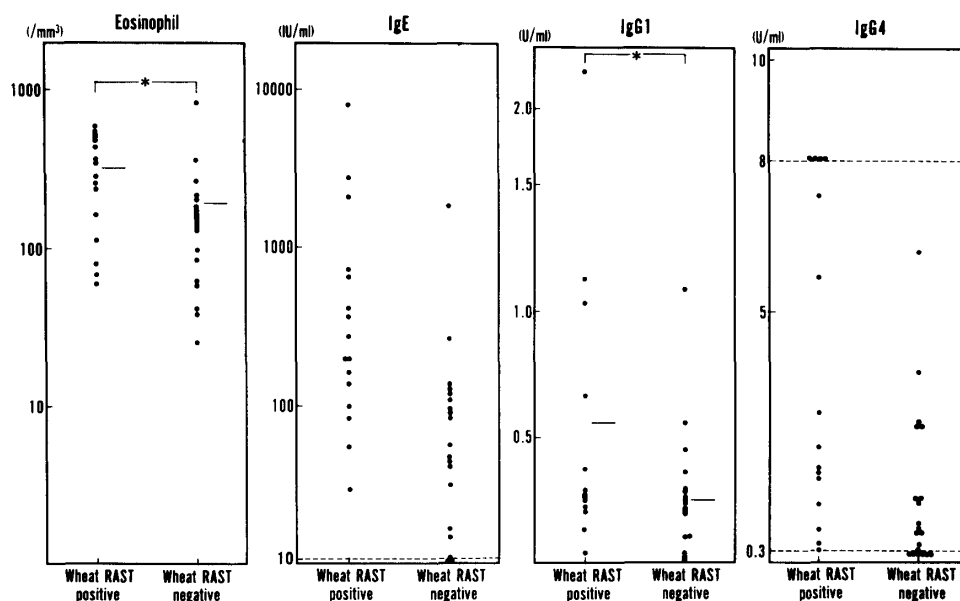


Fig. 2. Comparison of wheat RAST positive and negative workers.
(* $p < 0.05$), (— Mean), (-----) limit of sensitivity of assay.

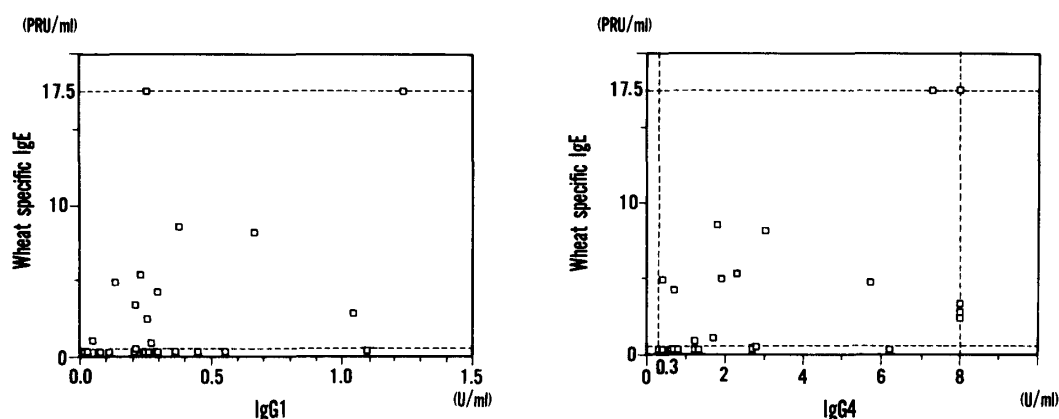


Fig. 3. Correlations of wheat specific IgE to IgG1 and IgG4.
(-----) limit of sensitivity of assay.

RAST positivity and allergy symptoms, as calculated by the χ^2 method ($p < 0.05$).

Workers were grouped according to RAST scores. The mean eosinophil level was $318.8 \pm 188.2/\text{mm}^3$ for the wheat flour RAST positive group and $178.3 \pm 175.6/\text{mm}^3$ for the negative group. Significantly higher ($p < 0.05$) eosinophil levels were observed in RAST positive cases as calculated using unpaired t -test. Total IgE levels were also elevated in wheat flour RAST positive cases, but statistical significance could not be calculated because two cases had levels below the measurable range. The mean IgG1 level was 0.55 ± 0.60 U/ml for the RAST positive group and

0.24 ± 0.25 U/ml for the negative group. IgG1 levels were significantly increased ($p < 0.05$) in RAST positive cases, as calculated using the unpaired t -test. Wheat specific IgG4 also seemed to be increased in those with positive RAST scores but statistical analysis was not possible because some values were in an unmeasurable range (Fig. 2).

Anti-wheat flour IgG subclass antibodies (IgG1 and IgG4) measured by ELISA showed no correlation with IgE. Wheat flour specific IgG1 and IgG4 seemed to correlate positively with wheat flour specific IgE, but statistical analysis was not possible because some values were outside of the

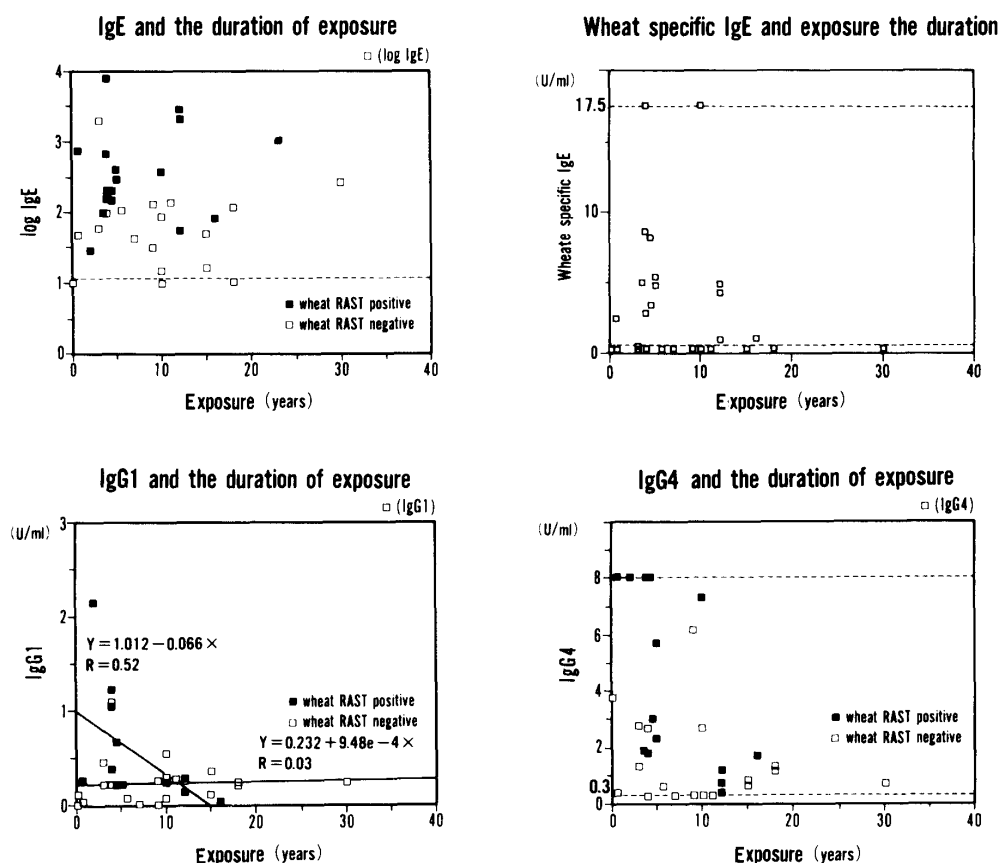


Fig. 4. Relations of exposure duration to total IgE, wheat specific IgE, IgG1 and IgG4. (-----) limit of sensitivity of assay.

measurable range (Fig. 3).

There was correlation between exposure duration and either total IgE or specific IgE. In wheat flour RAST-positive cases, IgG1 levels correlated negatively with duration of exposure ($R=0.52$). However, in RAST negative cases, there was no correlation ($R=0.03$). Similarly, there was a tendency for IgG4 levels and exposure duration to correlate negatively in RAST positive cases. But statistical evaluation was not possible because some IgG4 levels exceeded the measurable range (Fig. 4). We did not find a clear relation between IgG subclass levels and clinical symptoms. We also could not determine the contribution, if any, of IgG subclass antibodies to allergic symptoms.

The subjects of this study initially worked in poorly ventilated areas. Most symptomatic cases reported improvement after the installation of an air purifier (Fig. 5). Mean eosinophil levels, calculated from the data of workers No. 1, 2, 4, 5, 8, 10, 12, 18, 19 and 23, were $286.8 \pm 182.1/\text{mm}^3$ before and $227.7 \pm 188.8/\text{mm}^3$ after introducing

protective measures, showing no significant difference. Similarly, the mean IgE level before was 1375.5 ± 2365.0 IU/ml and after 903.1 ± 1972.4 IU/ml for workers No. 1, 2, 4, 5, 7, 8, 10, 12, 13, 18 and 19, showing a significant improvement as calculated by *t*-test ($p<0.05$). As to wheat flour RAST (PRU), some levels were not within measurable range, values in the detectable range seemed to improve. The mean IgG1 level before protective measures was 0.513 ± 0.403 U/ml, while that after was 0.338 ± 0.270 for workers No. 1, 2, 4, 5, 8, 10, 12, 13, 18, 19 and 23. Thus, a statistically significant difference was observed. The IgG4 level could not be calculated because some values were outside of the measurable range, but detectable levels did not appear to be significantly different.

There were no significant correlations, as calculated by the χ^2 method between mite and wheat flour RAST score ($p<0.05$), barley and wheat flour RAST scores ($p<0.05$), and rye and wheat RAST scores ($p<0.05$) (Fig. 6).

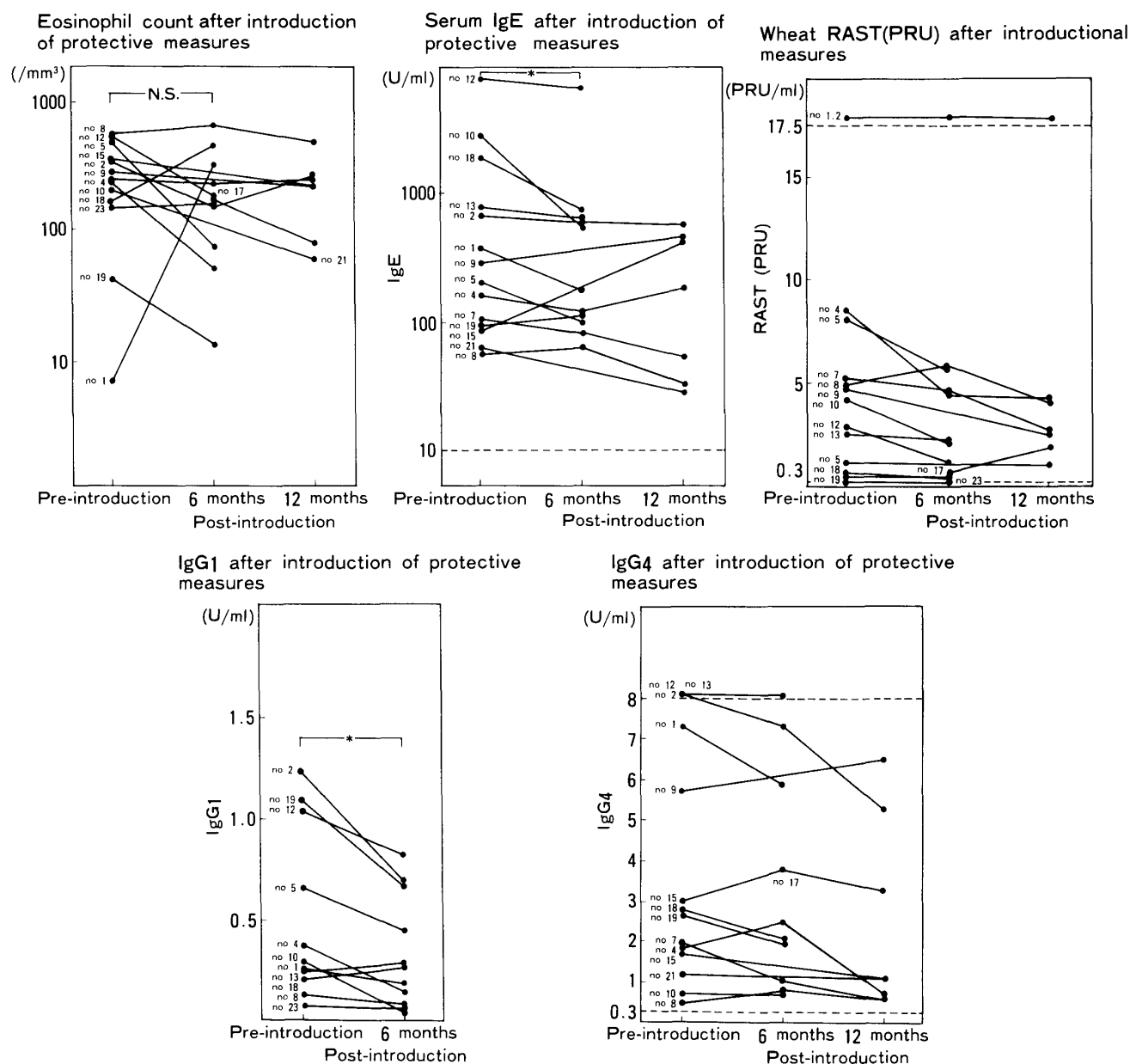


Fig. 5. Comparison of eosinophil, IgE, Wheat RAST, IgG1 and IgG4 before and after the introduction of protective measures, such as air purifiers and masks, in the work place.
 (* $p < 0.05$) (-----) limit of sensitivity of assay.

Certain enzymes used as baking additives, such as α -amylase and papain, have been suggested to be sensitizing agents¹⁰⁻¹². When α -amylase and papain RAST were measured in 13 cases, two (15.4%) were found to be both α -amylase and papain positive. We found that 15.4% of workers were sensitized to each of these baking additives.

DISCUSSION

Baker's asthma, baker's coryza and baker's eczema have been reported to affect 10-23% of workers in this field³. Based on our results, the incidences of these clinical symptoms appear to be comparable in Japan. Among the symptoms reported, nasal symptoms appear somewhat earlier than others. Rhinitis was the initial disorder in many earlier investigations, and this was also the

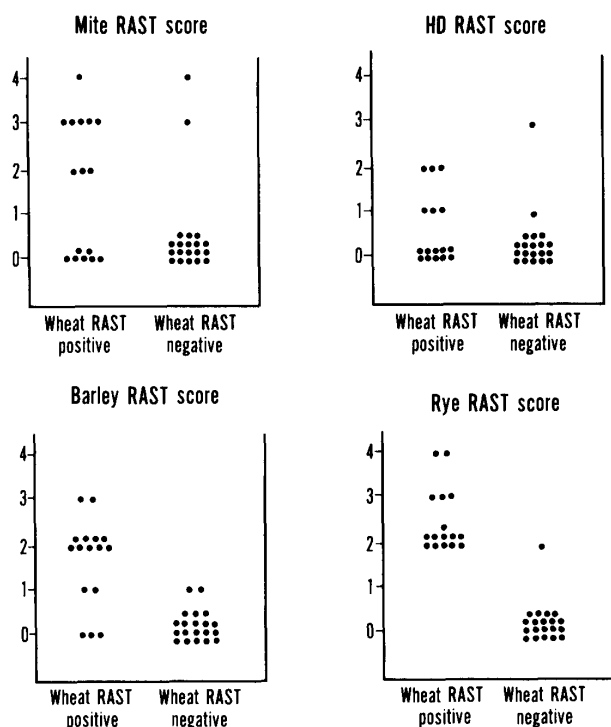


Fig. 6. Wheat RAST score and other RAST scores.

case in our study. The apparent decrease in the incidence of rhinitis with increasing duration of exposure cannot, however, be explained by our data.

It is interesting that those exposed to wheat flour for a long period of time do not always have severe symptoms. There is a possibility that those workers who develop severe symptoms quit their jobs. In other words, only workers who are not sensitized or who have minimal symptoms can continue their occupation. It is therefore very difficult to determine clear relations among exposure period, symptoms and numerous contributing factors such as serum IgE, wheat flour specific IgE, wheat flour specific IgG1 and IgG4.

In this study, we examined the distribution of IgG subclass anti-wheat flour antibodies and work-related symptoms. IgG1 is considered to be an anaphylactic antibody which causes allergic reactions identical to those of IgE, or contributes to the late asthmatic response¹⁴⁾¹⁵⁾. IgG4 is thought to be a blocking antibody capable of inhibiting IgE-mediated reactions, and it is said that antigen-specific immunotherapy is based on production of this antibody¹⁶⁾¹⁷⁾. Some authors have, however,

suggested that allergen-specific IgG4 is important in the production of allergy symptoms¹⁸⁾¹⁹⁾. It has also been reported that this can result from antigen exposure alone²⁰⁾²¹⁾. The roles of IgG subclass antibodies are therefore complicated and controversial. Our results indicate that elevation of wheat flour specific IgG1 is statistically significant in wheat flour RAST positive cases, and that it correlates negatively with duration of exposure. These results are in relatively good accordance with those reported in the literature²²⁾. Furthermore, IgG1 levels decreased after the institution of protective measures, suggesting that IgG1 plays an important role in allergic symptoms. The decreases in antibody levels in those who worked longer cannot, however, be explained by our data. The possibility exists that IgG1 is elevated only in the early exposure period, and that this response declines after reaching a certain level of allergen exposure.

Statistical analysis of IgG4 was not possible because some levels were in an unmeasurable range with the technique we used. There was, however, a tendency for IgG4 levels to be elevated in wheat flour RAST positive cases and there seemed to be a negative correlation with exposure duration.

These IgG subclasses may be thus taken only as an index of allergen exposure. Further studies are being undertaken to clarify the role of IgG subclass antibodies in bakers' allergy symptoms.

Among the wheat flour RAST positive cases, there was a tendency to be mite, barley and rye RAST positive as well. This suggests that atopic mechanisms contribute to wheat flour sensitization. In addition to the duration and intensity of exposure to the antigen, it has been suggested that individual factors, such as hereditary allergic predisposition, are responsible for sensitization to wheat flour. However, cross reaction is also a possibility in cases in which other RAST scores were positive.

Inhalation uptake of enzymes is reportedly associated with a high risk of developing allergic respiratory diseases. Various powdered enzymes are extensively used in baking to improve the quality of products. These baking additives also make the baking process shorter and more economical. α -amylase provides fermentable sugars

for yeast, improving loaf volume and texture. Papain improves flavor and texture. The frequency of sensitization to α -amylase was reported to be 24%, and that to papain 1%¹²⁾. We found that 15.4% of workers were sensitized to each of these baking additives, indicating that such enzymes must be taken into account in determining the etiology of so-called baker's asthma. Taken together, these data indicate that allergic symptoms result not from wheat flour allergy alone, but rather from a combination of allergies to various materials.

Allergies related to or stemming from a specific occupation provide an excellent opportunity to examine the immunologic mechanisms underlying atopic phenomena. We have focused on the clinical features of wheat allergy, which appears to be an atopic response to wheat flour that may be exacerbated to some extent by baking additives. The precise roles of various contributory factors remain to be elucidated. Other occupational allergies have also been reported in Japan and other Asian countries. As lifestyles and eating habits change throughout the region, these allergies are likely to become more prevalent. However, inhalation of and contact with such allergens can be minimized by proper ventilation, and the wearing of filter masks. Among the workers examined in this study, 34 continued in the same occupation whereas two (No. 3, No. 5) left their jobs because of severe symptoms. We feel that this is a subject which merits extensive future research.

CONCLUSION

The allergic symptoms of bakers cannot be explained by sensitization to wheat flour alone. Rather, these symptoms are a composite of allergies to various materials. Furthermore, atopic mechanisms contribute to symptom development. The results of this study indicate that IgG subclasses can serve only as an index of allergen exposure.

REFERENCES

- 1) Bonnevie, P.: Occupational allergy in bakery. "Occupational Allergy" (ed. by H.E. Stenfert Kreese N.V.), Leiden, Netherland, pp. 161-169, 1958.
- 2) Jimenez-Diaz, C., Lahoz, C. and Canto, G.: The allergens of mill dust. *Ann. Allergy* **1**, 519-525, 1947.
- 3) Schwartz, M.: Flour allergy. *J. Allergy* **18**, 341-350, 1947.
- 4) Castberg, T. and Sørensen, M.: Allergic examination of bakers and millers. *Acta. Allergol.* **1**, 283-296, 1948.
- 5) Kamidaira, T., Suetsugu, S. and Umeda, H.: Clinical and immunologic studies on patients with bakers' asthma. *Jpn. J. Allergol.* **35**, 47-59, 1986.
- 6) Sakamoto, Y., Asai, S., Taniguchi, T., Yamazaki, H. and Watanabe, H., et al.: A case of Bakers' asthma and a Review of 24 cases reported in Japan. *Nihon Kyobu Rinshou (Jpn. J. Chest Dis.)* **45**, 316-322, 1986.
- 7) Goldstein, G.B., Heiner, D.C. and Rose, B.: Studies of reagins to α -gliadin in a patient with wheat hypersensitivity. *J. Allergy* **44**, 37-50, 1969.
- 8) Pfeil, T., Schwabl, U., Ulmer, W.T. and König, W.: Western blot analysis of water-soluble wheat flour allergens. *Int. Arch. Allergy Appl. Immunol.* **91**, 224-231, 1990.
- 9) Revsbech, P. and Dueholm, M.: Storage mite allergy bakers. *Allergy* **45**, 204-208, 1990.
- 10) Flindt, M.L.H.: Allergy to alpha-amylase and papain. *Lancet* **30**, 1407-1408, 1979.
- 11) Baur, X., Fruhmman, G., Haug, B., Rasche, B. and Reiher, W.: Role of *Aspergillus* amylase in baker's asthma. *Lancet* **30**, 43, 1986.
- 12) Baur, X., Sauer, W. and Weiss, W.: Baking additives as new allergen in baker's asthma. *Respiration* **54**, 70-72, 1988.
- 13) Thiel, H. and Ulmer, W.T.: Baker's asthma. Development and possibility for treatment. *Chest* **78**, 400-405, 1978.
- 14) Ito, K., Kudo, K., Okudaira, H., Yoshinoya, S., Morita, Y., et al.: IgG1 antibodies to house dust mite and late asthmatic response. *Int. Arch. Allergy Appl. Immunol.* **81**, 69-74, 1986.
- 15) Nakagawa, T.: The role of IgG subclass antibodies in allergic reactions. *Immunol. Allergy Pract.* **9**, 453, 1987.
- 16) Nakagawa, T., Takaishi, T., Sakamoto, Y., Ito, K., Miyamoto, T. and Skvaril, F.: IgG4 antibodies in patient with house-dust-mite sensitive bronchial asthma. Relationship with antigen-specific immunotherapy in allergic disease. *Int. Arch. Allergy Appl. Immunol.* **71**, 122-125, 1983.
- 17) Nakagawa, T.: The role of IgG subclass antibodies in the response to immunotherapy in allergic disease. *Clin. Exp. Allergy* **21**, 289-296, 1991.
- 18) Parish, W.E.: The clinical relevance of heat-stable,

- short-term sensitizing anaphylactic IgG antibodies (IgG S-TS) and of related activities of IgG4 and IgG2. *Br. J. Dermatol.* **105**, 223-231, 1981.
- 19) Gwynn, C.M., Ingram, J., Almousawi, T. and Stanworth, D.R.: Bronchial provocation tests in atopic patients with allergen-specific IgG4 antibodies. *Lancet* **1**, 254-256, 1982.
 - 20) Husby, S., Larsen, F.S., Ahlstedt, S. and Svehang, S.E.: Humoral immunity to dietary antigens in atopic dermatitis. *Allergy* **41**, 386-391, 1986.
 - 21) Homburger, H.A., Mause, K., Sachs, M.I., O'Connell, E.J., Jacob, G.L. and Caron, J.: Serum IgG4 concentrations and allergen-specific antibodies compared in adults and children with asthma and nonallergic subjects. *J. Allergy Clin. Immunol.* **77**, 427-434, 1986.
 - 22) Tiikainen, U. and Klockars, M.: Clinical significance of IgG subclass antibodies to wheat flour antigens in bakers. *Allergy* **45**, 497-504, 1990.

製パン，製菓業従事者におけるアレルギー症状と関連因子に関する研究

東京医科大学第3内科

松村康広 新妻知行 伊藤久雄

小麦粉などを使用している製パン，製菓業従事者36人（男33，女3，平均年齢29.1歳）の臨床症状と症状発現に関すると考えられる因子について検討した。症状は鼻症状が13例，皮膚症状，眼症状，呼吸器症状がそれぞれ8例であった。44.4%の症例で小麦粉特異 IgE 抗体が陽性で，陽性者では好酸球数，IgE 抗体，小麦粉特異 IgG1抗体が有意に上昇しており，小麦粉特異 IgG4抗体も上昇傾向にあった。さらに暴露期間の長い者ほど小麦粉特異 IgG1抗体が低値で，小麦粉特異 IgG4抗体も同様な傾向にあった。環境整備後，IgE 抗体，小麦粉特異 IgG1抗体の減少が認められた。これら IgG サブクラスは抗原暴露の一つの指標と考えられたが症状発現への役割は明らかではなかった。小麦粉特異 IgE 抗体陽性者ではダニ，大麦，ライ麦にも陽性を示すものが多く，アトピー素因の関与が示唆された。さらに，15.4%の症例では α -アミラーゼやパepsinなどのような添加物質による感作も認められ，従事者のアレルギー症状は，種々の物質による複合感作であると考えられた。