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OCCUPATIONAL AND NON OCCUPATIONAL RESPIRATORY ALLERGY IN BAKERS

By

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Allergy to flour was studied by many authors (2, 3, 4, 7, 9, 16, 29, 33, 35, 39, etc.). However, few investigators used challenge tests as a diagnostic tool (20, 23, 35, 36). To us, challenge tests appeared particularly indicated in studying the allergy to flour since. 1) Many if not most allergic bakers display concomitant positive skin tests to various allergens (4, 5, 9, 16, 20, 29, 33, 40); in these subjects a careful anamnesis could occasionally distinguish between latent and manifest allergy. For instance, in bakers with paroxysmal dyspnea occurring only at the working place, a concomitant positive skin test to house dust expresses only a latent allergy; but in bakers with asthma attacks both at work and at home (even during holidays or leaves), allergic etiology may be difficult to assess. 2) Anamnesis and skin tests are not sufficient when studying the part played in flour allergy by its contaminants (arthropodes, fungi, bacteria). 3) In occupational respiratory allergy, challenge tests reproducing the spontaneous complaints are the most convincing diagnostic procedures (30, 31).

Modern equipment diminished considerably the incidence of allergy to flour (33), utilization of persulfate (41) was

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prohibited in most countries, but allergic bakers still exist since contact with flour dust is difficult to prevent.

We planned to investigate in subjects occupationally exposed to flour: 1) Allergy to flour and its main contaminant arthropodes as well as non occupational allergy to house dust, bacteria, fungi and pollen. 2) The various clinical forms of respiratory allergy encountered in bakers. Our study was designed as an investigation of clinical allergy and not as an epidemiologic one. Therefore, only usual clinical diagnostic methods were employed (anamnesis, skin tests, challenge tests).

MATERIAL

Forty-three consecutive subjects with occupational exposure to wheat flour and with allergic respiratory complaints were included in this study. Subjects occupationally exposed to grains were excluded from the study, with the exception of one subject, exposed both to wheat flour dust and wheat grains. These 43 subjects will be designed as bakers, though only 40 of them were actually bakers; three had managing positions in a bakery. Clinical diagnosis in these subjects was: allergic rhinitis (4 subjects), allergic rhinitis and bronchitis (12 subjects), allergic rhinitis and asthmatic bronchitis (13 subjects), allergic rhinitis and asthma (14 subjects). Diagnostic criteria: rhinitis as Dishoeck (8); allergic bronchitis¹: spasmodic cough with sputum elimination, eventually with chest tightness; allergic asthmatic bronchitis: mild paroxysmal dyspnea with chest tightness, cough and in most subjects with some expectoration; bronchial asthma: severe paroxysmal dyspnea having the character indicated by the Committee on the etiology of chronic bronchitis (6).

METHODS

a) *Anamnesis* was considered as very suggestive, suggestive or not suggestive for sensitization to a certain allergen (criteria in *Popa et al.* (31).

b) *Skin tests*. The following allergens were used: 1) *Flour*. Wheat flour was incubated 48 hours with physiologic buffered saline (pH 7.2); the supernatant was centrifugated 10' at 3,000 r.p.m., sterilised by passing through a Seitz filter and used in intradermal and inhalation tests. This concentrated allergen was kept in refrigerator at 4° C; fresh solutions were prepared every 21 days. For intradermal tests, first a 1/1,000 dilution (weight/volume) was used; if it

¹ We are not using the conventional criteria (6) for chronic bronchitis, because in any allergic disorder (*e.g.* bronchial asthma, urticaria), duration of symptoms has no diagnostic significance.

elicited no positive reaction, it was followed by a more strong concentration, *i.e.* 1/100 (dilution was made in physiologic buffered saline). 2) In the subject with concomitant occupational contact with wheat grain the Hollister-Stier, *Grain Mill Dust* was also employed (500 PNU/ml). 3) The main *arthropods* contaminating the flour in our country (27) are: *Tyroglyphus farinae* (class Arachnida, order Acarina), *Tenebroides mauritanicus*, *Tribolium castaneum*, *Calandra oryzae*, *Calandra granaria* (beetles—class Hexapoda or Insects, order Coleoptera), *Ephestia kühniella* and *Sitotroga cerealella* (moths—class Hexapoda, order Lepidoptera). With one exception, each was cultivated separately at the Entomology Laboratory of the Central Institutes of Agricultural Research (Bucharest). As *Calandra granaria* was cultivated with *Tribolium castaneum* and as no isolated culture of the former was available at that time, we prepared a mixed extract. A separate allergen from *Tribolium castaneum* was prepared from the respective beetle cultivated alone. All these arthropods were carefully separated from their nutrient media (grains) and allergen extraction proceeded as indicated by *Perlman* (28). For skin tests, arthropode allergens were used in a 1/100,000 dilution (*Feinberg* 10). 4) *Pollen*. Standard groups of Bencard Pollen Allergens (A_{12} as well as B_1 , B_2 , B_3 , B_8 , B_9 , B_{10} , B_{11}) were tested by the scratch method. The Pasteur Pollen ("Pollen de graminées") was employed together with Bencard pollen and used in intradermal testing (concentration 1/1,000,000 and 1/100,000 beginning with the highest dilution). 5) *House dust*, four standard bacterial groups (F_1 , F_2 , F_4 , F_5) and three standard mould groups (A_{13} , M_{10} , M_{11}) contained in the Bencard Skin Testing Cabinet. The original concentration of Bencard intradermal test solution was used, with the exception of bacterial allergens which were employed in a 1/10th weaker concentration. If a standard group elicited a positive reaction, its components were tested separately. Intestinal bacteria (most comprised in F_5 group, Bencard) as well as Hollister-Stier allergens were used in concentration of 20 millions bacteria/ml).

c) *Provocation tests*. Nasal and bronchial provocation tests were carried out as published before (30, 31) with one difference: each bronchial test was preceded by a control test with the corresponding diluent. Every subject was submitted to a set of challenge tests comprising the following allergens: flour, arthropode extracts and, with the exception of pollen, all other allergens provoking a positive intradermal response irrespective of any anamnesis suggestion. One subject had also a bronchial test to grain mill dust. Concentration of these allergens varied according to the route of administration (Table 1). For flour and arthropode allergens prepared in our laboratory control challenge tests were performed in subjects with allergic rhinitis and bronchial asthma having no occupational contact with them (7 subjects for each allergen); the highest concentrations from Table 1 were used. In the bakers, the route of administration was as follows: 1) rhinitis: nasal tests; 2) rhinitis and bronchitis: nasal and bronchial tests, provided the acetylcholine (AcCh) test was positive. Two subjects with negative AcCh test were submitted however to these tests. 3)

TABLE 1
Concentration of Allergens Used in Provocation Tests.

Provocation test	Grain mill dust	Flour	Arthropodes*	Non occupational allergens (% of the original conc. of Inhal. test vial)
Nasal	—	1%	0.1%—0.01%	10%
Bronchial	5,000—10,000§ PNU	1—20%†	1%	10%—100%‡§

* Testing with arthropodes began with a group test in concentration 0.1 per cent, comprising the seven arthropode extracts in the concentrations specified above. If a positive response was obtained, individual extracts were used, but in lower concentration (0.01 per cent), in order to point out the offending allergen.

§ The higher concentration was used only in subjects whose personal history was highly suggestive for sensitization to that allergen.

† Bronchial tests with flour began with 1 per cent concentration; it was raised at 10 per cent if no asthma attack occurred after 60'. Two days afterwards, 20 per cent concentration was employed if the 10 per cent had given no positive response.

Rhinitis and asthmatic bronchitis: bronchial tests and in most cases, for most allergens, nasal tests also. 4) Rhinitis and asthma: bronchial tests and, in 5 subjects, nasal tests to flour, too.

d) *Acetylcholine inhalation tests* were performed with the same nebulizer (Dräger Aerolette) and using the same criteria of positivity as bronchial provocation tests (31). All subjects with bronchitis and asthmatic bronchitis were submitted to these tests. Three asthmatic subjects had also an AcCh test. Subjects with ventilatory impairment were given Novodrin² and registration of spirographic values ($FEV_{1.0}$) followed after 20'; at least 10 per cent $FEV_{1.0}$ augmentation was required for a test to be considered as positive.

e) *Spirographic values* were recorded in all subjects the day they were examined for the first time. For the sake of brevity the spirographic values will be designed as "normal" or "ventilatory obstructive impairment" ($C.V. \times 100/VEMS$ less than 70 per cent).

² Novodrin = DL-3,4-dioxyphenyl-ethanolisopropylamine sulphate 1 per cent (VEB Chemisches Werk, Berlin-Grünau, D. D.R.).

TABLE 2
Skin Tests with 1 per Cent and 0.001 per Cent Arthropode Extracts.

Subjects	Flour		Tenebroides mauritanicus		Calandra oryzae		Tribolium castaneum		Calandra g. Tribolium c.		Ephesia kühniella		Sitotroga cerealella		Tyroglyphus farinae	
	No.	Pos. (%)	No.	Pos. (%)	No.	Pos. (%)	No.	Pos. (%)	No.	Pos. (%)	No.	Pos. (%)	No.	Pos. (%)	No.	Pos. (%)
Control	50	2 (4)	50	6 (12)	50	5 (10)	50	7 (14)	50	7 (14)	50	7 (14)	50	4 (8)	50	6 (12)
Allergic bakers	43 (100)	43	32	15 (46)	32	14 (43)	32	17 (53)	32	17 (53)	43	30 (69)	32	5 (46)	32	14 (43)

Only immediate reactions (at 30') were taken into consideration Control subjects: non allergic subjects and not occupationally exposed to flour.

TABLE
Provocations

No.	Subject	Diagnosis	Flour		Arthropodes	
			N	B	N	B
1.	G. J.	Allergic rhinitis	—(10%)	×	TC	×
2.	D. C.	Idem	+(1%)	×	—	×
3.	R. H.	Rhinitis vasomotoria	—(10%)	×	—	×
4.	A. A.	Idem	—(10%)	×	—	×
5.	I. M.	Rhinitis bronchitis (allergen known)	+(1%)	×	—	×
6.	E. T.	Idem	+(1%)	×	SC	×
7.	C. E.	Idem	+(1%)	—(20%)	TG CG	—
8.	V. G.	Idem	+(1%)	×	TF	×
9.	N. A.	Idem	+(10%)	—(20%)	—	—
10.	P. E.	Idem	—(10%)	—(20%)	TM	—
11.	T. E.	Idem	—(10%)	—(20%)	TM	—
12.	D. I.	Idem	+(1%)	—(20%)	—	—
13.	P. D.	Idem	—(10%)	—(20%)	—	—
14.	M. I.	Idem	—(10%)	—(20%)	—	—
15.	F. I.	Idem	—(10%)	—(20%)	—*	—
16.	I. J.	Rhinitis, asthmatic bronchitis	+(1%)	+(20%)	—	—
17.	C. M.	Idem	+(1%)	+(20%)	—	—
18.	B. C.	Idem	+(1%)	+(20%)	—	—
19.	S. G.	Idem	+(1%)	+(20%)	—	—
20.	Z. G.	Idem	+(1%)	+(20%)	—	—
21.	A. S.	Idem	×	+(20%)	—*	—
22.	G. G.	Idem	×	+(20%)	—	—
23.	T. A.	Idem	+(10%)	+(20%)	—*	—
24.	C. D.	Idem	×	+(20%)	—*	—
25.	M. G.	Idem	—(1%)	+(20%)	—*	—
26.	G. I.	Idem	×	+(20%)	—*	—
27.	M. N.	Idem	+(1%)	+(20%)	—	—
28.	T. P.	Idem	—(10%)	—(20%)	—	—

Tests.

House dust		Bacteria		Fungi		AcCh	Spiro- graphic values
N	B	N	B	N	B		
—	×	Staph.	×	×	×	×	N
—	×	—	×	—	×	×	N
—	×	—	×	—	×	×	N
—	×	—	×	×	×	×	N
—	×	×	×	—	×	—	N
—	×	×	×	—	×	—	N
—	×	—	×	×	×	—	N
—	—	—	—	—	—	—	N
—	—	—	×	×	×	+	N
—	—	×	×	×	+	+	N
—	—	×	×	×	×	—	N
—	—	Staph.	—	×	×	+	N
—	—	Staph.	—	×	×	+	N
—	—	Strept.	—	×	×	+	N
×	×	Staph.	—	×	×	+	N
—	—	—	—	—	—	?	N
—	—	×	—	×	—	+	N
×	×	—	—	—	—	+	N
—	—	×	×	×	×	+	N
—	—	×	×	×	×	+	N
—	—	×	×	×	×	+	N
—	—	—	—	—	—	+	N
—	—	—	—	—	—	+	N
—	—	—	—	—	—	+	N
—	—	—	—	×	×	+	N
—	—	×	×	—	—	+	N
—	—	—	—	×	×	+	N
—	—	Prot.	—	—	—	+	N

No.	Subject	Diagnosis	Flour		Arthropodes	
			N	B	N	B
29.	P. G.	Rhinitis,	+(1%)	+(1%)	×	—
30.	B. M.	asthma				
31.	I. T.	Idem	+(1%)	+(10%)	×	—
32.	D. M.	Idem	+(1%)	+(1%)	×	—
33.	D. M. T.	Idem	—(1%)	+(10%)	×	—
34.	B. C.	Idem	—(1%)	+(10%)	×	—
35.	I. M.	Idem	×	+(1%)	×	—
36.	B. I.	Idem	×	+(1%)	×	—
37.	I. G.	Idem	×	+(1%)	×	E. K.
38.	S. M.	Idem	×	+(10%)	×	—*
39.	O. I.	Idem	×	+(10%)	×	—*
40.	A. G.	Idem	×	+(10%)	×	—*
41.	P. M.	Idem	×	—(20%)	×	—*
				+ Grain mill dust (10,000 PNU)		
42.	P. C.	Idem	×	—(20%)	×	E. K.
43.	G. A.	Idem	×	—(20%)	×	—

* = Provocation tests carried out only with *Ephestia kühniella*.

± = Positive.

— = Negative.

Staph. = *Staphylococcus*.

Strept. = *Streptococcus*.

Hem. = *H. influenzae*.

Prot. = *Proteus*.

V. I. = Ventilatory impairment.

? = Cough prevented correct AcCh testing.

RESULTS

Anamnesis was very suggestive for flour sensitization in all subjects. In 16 subjects it indicated polysensitization (allergic syndromes occurring during holidays or leaves too); these subjects suffered from rhinitis ± bronchitis (7 subjects), rhinitis and asthmatic bronchitis (4 subjects), rhinitis and asthma (5 subjects).

(cont.)

House dust		Bacteria		Fungi		AcCh	Spiro-graphic values
N	B	N	B	N	B		
—	—	Hem.	—	—	—	+	N
×	—	×	×	×	×	+	N
×	—	×	—	×	—	×	N
×	—	×	—	×	×	+	N
×	—	×	—	×	—	+	N
×	×	×	×	×	—	×	N
×	—	×	—	×	—	Nov.	V. I.
×	—	×	—	×	—	×	N
×	—	×	—	×	—	Nov.	V. I.
×	—	×	—	×	—	×	N
×	—	×	×	×	×	Nov.	V. I.
×	+	×	×	×	×	Nov.	V. I.
×	—	×	—	×	—	×	N
×	—	×	×	×	—	Nov.	V. I.
×	—	×	Staph.	×	×	Nov.	V. I.

Nov. = Bronchodilator test with Novodrin.

TC = *Tribolium castaneum*.SC = *Sitotroga cerealella*.CG = *Calandra granaria*.TF = *Tyroglyphus farinae*.TM = *Tenebroides mauritanicus*.EK = *Ephestia künniella*.

In parantheses: Concentrations w/v of flour and arthropode allergens.

Skin tests. 1) All subjects had a positive intradermal test to flour (1/1,000 or 1/100). 2) All subjects had at least two positive skin tests to the arthropode extracts (Table 2); 32 subjects tested to *Ephestia* had 22 positive skin tests. With this correction, skin tests to arthropodes presented in Table 2 amount to 96, resulting a mean of 3 positive tests per subject. The difference between control subjects and bakers is statistically significant at a < 0.05 (in some cases $p < 0.01$) for both

TABLE 4
Clinical Features.

Diagnosis	No. of sub- jects	Sex		Length of occupational exposure (years)			Mean	Age at onset mean* (range)
		♂	♀	0-5	5-10	> 10		
Occupational allergy	35	21	14	6	11	18	12.2	40.1 (23-54)
- Rhinitis ± bronchitis	10	4	6	2	5	3	9.1	34.1 (23-41)
- Rhinitis and asthmatic bronchitis	12	8	4	1	3	8	13.2	42.1 (32-54)
- Rhinitis and asthma	13	9	4	3	3	7	14.0	43.0 (26-50)
Non occupational allergy	8	4	4	2	1	5	14.2	40.1 (24-54)
- Rhinitis ± bronchitis	6	2	4	2	1	3	11.2	39.2 (24-48)
- Rhinitis and asthmatic bronchitis	1	1	0	0	0	1	18.0	36.0
- Rhinitis and asthma	1	1	0	0	0	1	30.0	54.0
Total	43	25	18	8	12	23	12.7	40.1 (23-54)

* Arithmetic mean.

flour and arthropode extracts. 3) Fortyone per cent of the subjects (18/43) reacted to intradermal tests with 1/100,000 "Pollen de graminées" (Pasteur). None had a positive scratch test to Bencard allergens. 4) House dust elicited a positive i.d.r. in all but three subjects (93 per cent). Positive i.d. tests to bacteria were noted in 29/43 subjects (67 per cent); these subjects had one to four positive tests. Moulds evoked a positive test in 24/43 subjects (55 per cent); they had one to three positive tests.

Provocation tests. Table 3 presents the results of nasal and bronchial tests in each subject. In the same table are included the acetylcholine tests and the spirographic values.

Clinical features, according to their etiology, are shown in Table 4.

DISCUSSION

Allergy to flour. Anamnesis and skin tests seemed to indicate that all our subjects were allergic to flour. However, provocation tests failed to substantiate this etiology in 12 subjects (27 per cent): four reacted only to an insect extract, five only to non occupational allergens (bacteria) and three to no challenge test. In these 12 subjects, flour acted as an irritant; evidently, anamnesis could not separate the irritative from the sensitizing action. This is a most common fact in subjects occupationally exposed to substances or dusts having both an irritating and sensitizing activity (31). Stresemann recently reported (35) that only 60 per cent of bakers with positive skin tests had positive nasal or bronchial provocation tests, an incidence similar to that we found (73 per cent).

A most important fact in provocation tests is to use a non irritant diluent and allergen, and in (very) mild bronchial asthma (chronic asthmatic bronchitis), a strong concentration of allergen (32). Control tests for flour diluent and for flour allergen were always negative. The 20 per cent concentration of flour allergen was characterically required by the subjects with chronic asthmatic bronchitis due to flour (see "Clinical syndromes").

In contrast with bronchial tests, in nasal tests no attempt was made to establish a threshold concentration for flour. However, as Table 3 clearly points out, in most cases nasal sensitivity is higher than bronchial one (patients 17 to 29). There were only two exceptions (patients 9 and 23) who required a higher than usual flour concentration (10 per cent); this fact may account for the three negative nasal tests in subjects with allergic rhinitis and positive bronchial tests to flour (patients 25, 33, 34).

Allergy to grain mill dust. In the subject with concomitant occupational exposure to flour and wheat grains, bronchial test was positive to grain mill dust and negative to flour 20 per cent. This rather surprising fact is, however, in agreement with 1) Personal observations: a) from two asthmatic silo workers only one reacted to both flour (20 per cent) and grain mill dust (10,000 PNU); b) in flour allergic bakers, (three reacting to 20 per cent flour and one to 1 per cent flour) it was impossible to evoke a bronchial obstruction with 10,000 PNU grain mill dust; c) a similar observation concerns a subject with positive bronchial test to Bencard flour (1 per cent) but with no reaction to Bencard grain mill dust 1 per cent). 2) Data reported by Klunker (18). Further studies are needed with various concentrations and fractions of flour and grain dust allergens before any relationship between them could be either supported or denied.

Allergy to arthropodes. Our subjects were sensitive to *Tribolium castaneum*, *Tribolium castaneum* and *Calandra granaria*, *Tenebroides Mauritanicus*, *Sitotroga cerealella*, *Ephesio kühniella* and *Tyroglyphus farinae*. Sensitization to arthropode contaminants of the flour was previously assessed by intradermal, prick or "épicutaneo reaction" and rarely by challenge tests (19, 23, 36). Skin tests disclosed that allergic bakers had more frequently positive skin tests to the insects and acarina contaminating the flour than control nonallergic subjects (each subject had three positive tests—arithmetic mean-). A manifest allergy (14) could be demonstrated in 8 subjects (18 per cent). Without provocation tests, an overevaluation of

the arthropode allergy would have been unavoidable. Provocation tests allowed to single out the offending allergen. Sensitization to arthropodes was associated but in 2 cases with sensitization to flour: in both subjects insect sensitization represented the only causative allergen.

Part of the arthropodes considered in our series as offending allergens were already known to produce respiratory allergy in bakers or general population: *Tyroglyphus farinae* (37), *Tribolium castaneum* (3), *Calandra granaria* (17, 34), *Ephestia küchniella* (5, 16, 23, 24, 25, 26). We could not find any reference concerning sensitization to *Tenebroides Mauritanicus* and *Sitotroga cerealella*.

Allergy to other arthropodes contaminating the flour was presumed, suggested or demonstrated by various authors (1, 5, 7, 12, 13, 17, 19, 21, 22, 36, 39).

Pollen allergy. Anamnesis failed to indicate in any subject, even in those with positive i.d.r. that pollen might act as an allergen. As our subjects have already been submitted to many challenge tests, we deliberately refrained from provocation tests with another allergen not suggested by anamnesis. Others reported a similar incidence of pollen allergy (skin tests) in allergic bakers (5, 9); *Schwartz* (33) found three bakers with allergy to flour and seasonal (pollen) rhinitis.

Allergy to house dust and bacteria. There were 93 positive skin tests to these allergens. In 9 cases only (~ 10 per cent) provocation tests were positive: five to staphylococcus (patients 1, 13, 14, 15, 43) and, one each to house dust (patient 40), streptococcus (patient 14), *Proteus* (patient 28), *Haemophilus influenzae* (patient 29); a subject was sensitized to both *Streptococcus* and *Staphylococcus* (patient 14). In every subject with positive challenge tests the respiratory complaints persisted during holidays or leaves. However, there were other eight subjects whose respiratory complaints never cleared completely after long lasting leaves (infection?). As remarked by *Pestalozzi & Schnyder* (29), asthmatic bakers may offer a less clear cut relation between respiratory complaints and exposure to flour than bakers with rhinitis. Provo-

cation tests may help considerably in distinguishing the non allergic contributing factor, e.g. infection from the allergic determinant in an allergic baker with frequent respiratory complaints outside the working place.

Some of the *moulds* we used in skin and challenge tests are encountered also in the atmosphere of bakeries (38). None of them could be incriminated in the etiology of respiratory allergy syndromes in the bakers under study. *Smutfungi* (15) were not investigated in these subjects.

Acetylcholine inhalation test. Two comments only about this test: in subjects with chronic asthmatic bronchitis, it was necessary to nebulize 1 per cent AcCh 3' to 5' in order to obtain a positive bronchial reaction. In allergic bronchitis, AcCh nebulization lasted 5'; in 6 subjects the test was positive but the FEV_{1.0} diminished with 15–20 per cent and the clinical signs of bronchospasm were mild. In the remaining 5 subjects the test was negative. In the asthmatic subjects under study, as well as in other asthmatic subjects, the test always gave us streng positive results. Though the AcCh test was non quantitated, it resulted that cholinergic hyperreactivity seemed to parallel the clinical severity of the various bronchial allergic syndromes.

Clinical Features in Bakers with Respiratory Allergy

The present study had no epidemiologic character. All statistical data concerning age, sex, length of occupational exposure do not concern a population submitted to identical environmental factors and selected at random. Thus only brief comments will be made.

Length of occupational exposure. Rhinitis and bronchitis appeared after 9.1 years of working while bronchial asthma after 14.0 years; in this regard chronic asthmatic bronchitis resembled much bronchial asthma (2, 13). All our subjects had rhinitis: it was always (alone or associated to the bronchial syndrome) the first to appear. Any difference existing in the length of exposure till the first respiratory complaint

appeared was not due to rhinitis but to the bronchial syndrome. In other words, bronchial asthma did not appear later because many years elapsed between onset of rhinitis and onset of asthma. Bronchial asthma and asthmatic bronchitis appeared later because subjects who were more prone to develop a bronchial allergy required a longer interval of exposure than those whose allergic manifestations remained at the upper respiratory level or, if involving the bronchi, did not exceed a mild form (bronchitis). Sex (*vide infra*) might be one factor determining this surprising phenomenon. Other authors have also reported that rhinitis occurred after a shorter interval of working than asthma (5, 20, 29, 33, etc).

Age at onset. The occupationally as well as the non occupationally sensitized bakers had the same age at the onset of their respiratory complaints: 40 years. Rhinitis and bronchitis due to flour or arthropode allergy began at an earlier life moment (34.1 years) than asthmatic bronchitis (42.1) or asthma (43.0 years). Most of our cases of non occupational sensitization were due to bacteria; with one exception (a woman, 24 years old), all other subjects had more than 33 years at the onset of their allergic syndrome (similar observation in other personal cases of allergic bacterial asthma).

Sex. Rhinitis $\pm$ bronchitis (16 cases) occurred more frequently in females (10 cases) than in males. The contrary would seem to occur in asthmatic bronchitis and asthma (19 males and 8 females).

Clinical syndromes. Diagnoses of allergic rhinitis and bronchial asthma are accepted by all authors and deserve no particular comment.

In *allergic bronchitis* bronchial tests remained negative (insufficient allergen or predominant mucosal reaction?), supplying no etiologic information. Fortunately, allergic bronchitis was associated with rhinitis and nasal tests could be used for etiologic diagnosis in all but one subjects.

The term *asthmatic bronchitis* was employed in various senses. We simply meant a (very) mild bronchial asthma. For the internist or chest physician, asthmatic bronchitis may

be a confusing name and should be avoided. For the allergist, it might have a special meaning: a low bronchial sensitivity to allergens (32). For instance, in the bakers investigated it pointed to the necessity of employing high concentrations of flour extract (20 per cent). In asthmatic bronchitis, if high concentrations of allergen³ are not used, bronchial obstruction cannot be induced, the challenge test becomes false negative and etiologic diagnosis is overlooked (32). Had we considered asthmatic bronchitis as a "classical" bronchial asthma, we would have limited ourselves to the concentrations of flour usually employed in this syndrome (1 per cent or 10 per cent flour). In such a case it would have been impossible to diagnose "allergic asthma due to flour".

Subjects with asthmatic bronchitis resemble the hay fever subjects challenged with pollen by *Feinberg* (11); the latter subjects had a much lower bronchial sensitivity than subjects with bronchial asthma. Asthmatic bronchitis links "classical" bronchial asthma with allergic bronchitis. There is no clear cut borderline neither between allergic bronchitis and asthmatic bronchitis nor between asthmatic bronchitis and bronchial asthma (*e.g.* some subjects with asthma required a flour concentration of 1 per cent while others, 10 per cent, close to the subjects with asthmatic bronchitis).

As stressed elsewhere (32) there is no need to have one more ill defined term (asthmatic bronchitis), besides that of bronchial asthma. We used the term asthmatic bronchitis only to emphasize some peculiar aspects of a clinical form of bronchial asthma.

Summing up, in bakers with respiratory allergic complaints, various concentrations of flour (and other allergens) should be used in challenge tests, according to the route of administration—nasal or bronchial—and the clinical features—(*e.g.* typical or mild bronchial asthma).

³ In patients 13, 14, 15 (allergic bronchitis), 29 and 29, bronchial tests remained negative in spite of using the highest commercial concentrations of bacteria available (2,500 mil./ml—Bencard, and 2,000 mil./ml—Hollister-Stier).

SUMMARY

Allergy to flour, to seven arthropodes contaminating the flour, as well as to pollen, bacteria and moulds was investigated in 43 bakers with allergic complaints; all had rhinitis alone or associated with bronchitis, asthmatic bronchitis or bronchial asthma. Etiologic (allergologic) diagnosis relied on anamnesis, skin tests and challenge tests (nasal and bronchial). It resulted that the offending allergens were flour (31 subjects, including one baker allergic to mill dust), arthropodes (8 subjects—4 sensitized also to flour), house dust (one subject, sensitized also to flour). In 3 subjects it was not possible to find out the causative allergen.

The authors discuss the necessity of performing challenge tests with various allergens, in various concentrations; in mild bronchial asthma (chronic asthmatic bronchitis) bronchial testing required stronger concentrations of allergens than in typical bronchial asthma.

REFERENCES

1. *Ancona, G.*: Asma epidemico da "pediculoides ventricosus". Il Policlinico (Sez. Med.) 30, 3, 1923.
2. *Baagöe, K.*: Mehlidiosyncrasie als Ursache von vasomotorischer Rhinitis and Asthma. K.. Wschr. 12, 792, 1933.
3. *Bernton, H. S. & Brown, H.*: Insects as potential sources of ingestant allergens. Ann. Allergy 25, 381, 1967.
4. *Bounewic, P.*: Occupational allergy in bakers. In: Occupational Allergy, Springfield, Ch. C. Thomas, 1958.
5. *Charpin, J., Scarbouchi, J., Blanc, M. & Bekka, S.*: Etude allergologique chez les travailleurs de la farine. Rev. franç. d. allergie 4, 69, 1964.
6. *Committee on the Etiology of Chronic Bronchitis*: Definition and classification of chronic bronchitis for clinical and epidemiological purposes. Lancet I, 775, 1965.
7. *Diedrichs, W.*: Quoted by (21).
8. *Dishoeck, H. A. E.*: Überempfindlichkeit bei Hals, Nasen, Ohrenkrankheiten in: Hansen, K.: Allergie, Stuttgart, G. Thieme, 1957.
9. *Dishoeck, H. A. E. & Roux, D. J.*: Sensitization to flour and flour illness among flour workers. J. Hygiene 39, 674, 1939.
10. *Feinberg, S. M., Feinberg, A. R. & Pruzansky, J. J.*: Insect allergy. A com-

- mon cause cause of hay fever and asthma. *Proceed. III-rd Internat. Congress of Allergology* p. 293; Ed. Halpern, B. N., Holtzer, A. (eds.): Flammarion, Paris, 1958.
11. *Feinberg, S. M., Stier, R. A. & Grater, W. C.*: A suggested quantitative evaluation of the degree of sensitivity of patients with ragweed pollinosis. *J. Allergy* 23, 387, 1952.
 12. *Frankland, A. W.*: Sitophilus sensitivity as a cause of bakers asthma. *Acta allergol.* 21, 281, 1966.
 13. *Frugoni, C. & Ancona, G.*: Ulteriori studi sull'asma bronchiale. II Policlino (Sez. Med.) 32, 161, 1925.
 14. *Hansen, K.*: Allergie, Stuttgart, G. Thieme, 1957.
 15. *Harris, L. H.*: Allergy to grain dusts and smuts. *J. Allergy* 10, 327, 1939.
 16. *Herxheimer, H.*: Die Entwicklung von Mehlempfindlichkeit der Haut bei Bäckerlehrlingen und Bäckern. *Klin. Wschr.* 45, 481, 1967.
 17. *Jimenez-Diaz, G., Lakoz, C. & Canto, G.*: Quoted by (25).
 18. *Klunker, W.*: Zur Frage der Ätiologie und Pathogenese des sogenannten Bäcker- und Müllerasthmas. *Schw. med. Wschr.* 87, 714, 1957.
 19. *Lunn, J. A.*: Millworkers' asthma allergic responses to the Grain Weevil (*Sitophilus Granarius*). *Brit. J. Industr. Med.* 23, 149, 1966.
 20. *Lupu, N. G., Paun, R., Popesco, I. G., Zamfiresco-Gheorghiu, M., Olaru, C. & Iota, C.*: Contributions à l'étude de la sensibilisation allergique chez les meuniers et les boulangers. *Comptes rendus, t. I. 1^{er} Congrès Internat. d'allergie alimentaire et digestive, Vichy, 1963.*
 21. *Michel, H.*: Occupational sensitization of the upper and lower air passages by organic types of dust. In: *Occupational allergy*, Springfield, Ch. C. Thomas, 1958.
 22. *Maunsell, K., Wraith, D. G. & Cunningham, A. M.*: Mites and house-dust allergy in bronchial asthma. *Lancet* I, 1267, 1968.
 23. *Morichau-Beauchant, G. & Brisson, J.*: Le rôle d'un lépidoptère en allergie respiratoire. *Rev. franç. d'allergie* 2, 84, 1962.
 24. *Morichau-Beauchant, G., Brisson, J. & Dajcan-Falette.*: Importance relative de l'allergie à Pèphestia. *Rev. franç. d'allergie* 4, 26, 1964.
 25. *Morichau-Beauchant, G. & Nandin Vinot, G.*: L'asthme aux mites de la farine et des grains. *Presse Méd.* 63, 1439, 1957.
 26. *Morichau-Beauchant, G., Nandin Vinot, G.*: Asthmes aux mites de la farine et des grains. *Presse Méd.* 66, 1872, 1958.
 27. *Paulian, Fl., Alexandri, Al., Constantinescu, Gh., Ceiannu, V., Danet, Gh., Motoi, E., Severin, V., Snagovcanu, C., Tircomnicu, M.*: *Protectia plantelor.* Bucuresti, Ed. Agrosilvică, 1959.
 28. *Perlman, F.*: Insects as inhalant allergens. *J. Allergy* 29, 302, 1958.
 29. *Pestalozzi, C. & Schnyder, U. W.*: Zur Frage der Bäcker-rhinitis und Bäckerasthmas. *Schw. Med. Wschr.* 85, 496, 1955.
 30. *Popa, P. & Al-George, S.*: Nasal provocation tests in allergic perennial rhinitis; a preliminary study. *Ann. Allergy* 27, 45, 1969.

31. *Popa, V., Teculescu, D., Stancescu, D. & Gavrilescu, N.*: The value of inhalation tests in perennial bronchial asthma. *J. Allergy* 42, 130, 1968.
32. *Popa, V., Teculescu, D., Al-George, S. & Stancescu, D.*: Etiologic diagnosis in mild bronchial asthma (chronic asthmatic bronchitis) with allergic rhinitis. To be published.
33. *Schwartz, M.*: Flour allergy. *J. Allergy* 18, 341, 1947.
34. *Spoujilch, V.*: *Discussion au rapport*: Etiologie des maladies allergiques, par Pasteur Valléry-Radot, Wolf fromm, R. (p. 168), in: Symposium sur l'allergie, Beograd, Ed. Académie Serbe des Sciences, 1957.
35. *Stresemann, E.*: Results of bronchial testing in bakers. *Acta allergol.* 22 (suppl. 8), 99, 1967.
36. *Storm van Leeuwen, C., Bien, Z. & Farckamp, H.*: Experimentelle allergische Krankheiten (Asthma bronchiale, Rhinitis vasomotoria). *Z. Imm. Forsch.* 40, 552, 1924.
37. *Vorhorst, R.*: Basic facts of allergy. Leiden, H. E. Stenfert-Kroese, 1962.
38. *Werff, P. J. van der*: Mould fungi and bronchial asthma. Leiden, H. E. Stenfert Kroese, 1958.
39. *Wittich, F.*: Quoted by (19).
40. *Wolf fromm, R., Gervais, P. & Herman, D.*: Définitions et critères de l'asthme professionnel. *Poum. coeur* 22, 453, 1966.
41. *Zitzke, E.*: Die Ursache des Bäckerekezems. *Dtsch. Med. Wschr.* 60, 642, 1934.