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data are based only on subjective reports. However, even in an objective challenge situation, there is no single standard test to diagnose food-induced wheeze, because of the different immunological (and other) mechanisms involved, the varying interval between exposure and effect, dependence on the coexistence of other triggers, and the variety of outcome measures.[9]

The association between food intolerance and ethnic group in our study is strongly supported by laboratory studies based on double-blind food challenges, using lung function and bronchial responsiveness as outcomes (see review[9]). A variety of agents, including potential allergens, chemical agents, and physical agents (such as ice-cold drinks), may be responsible for intolerance among South Asian children with asthma.[6,7,9] No convincing mechanism has been proposed. The only common feature is ingestion, which suggests that mechanism must involve the upper gastrointestinal tract and may therefore involve neural (vagal) reflex phenomena or mediator release, rather than a direct effect of ingested agents on the airways. Nonatopic mechanisms may explain the greater prevalence of wheeze in migrant populations than in their parent populations in less developed countries.[10] However, the fact that, at age 6 to 9 years, hayfever and eczema were more prevalent among children reporting food-induced wheeze than among other wheezers suggests that IgE-mediated mechanisms contribute.

The findings that food as a trigger of wheeze was associated both with more severe symptoms and with South Asian ethnicity might partly explain the excess of healthcare utilization by wheezy children of South Asian origin in the UK.[1] We have confirmed the association between food-induced wheeze and healthcare utilization in this study.

The prognosis of preschool wheeze was worse among children reporting food intolerance, independently of the severity of wheeze (frequency of attacks), as previously reported in a retrospective survey.[5]

In conclusion, this is the first population-based study to show the excess prevalence of food-related wheeze in young children of South Asian origin born in the UK. The fact that reported food intolerance was associated with both the severity and persistence of wheeze makes it an important marker of clinically significant disease. Research into the mechanisms involved might lead to clues concerning early mechanisms in childhood asthma.

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Changes in specific IgE and IgG and monocyte chemoattractant protein-1 in workers with occupational asthma caused by diisocyanates and removed from exposure

To the Editor:

Workers with occupational asthma (OA) generally show improvement in symptoms and lung function after being removed from exposure, although the majority are left with permanent asthma and airway inflammation even several years after diagnosis. Few studies have examined changes in specific antibodies to agents causing OA after removal from exposure. The mean half-life of specific IgE antibodies to snow crab was 20 months[1] and, to tetrachlorophthalic anhydride, 1 year.[2] Tee et al[3] reported that the half-life for specific IgE reactive with diisocyanate human serum albumin (HSA) measured by RAST ranged from 5 to 7 months. Park et al[4] found that the mean half-life to isocyanates was 3.9 years in the case of specific IgE and 4.5 years for specific IgG. Levels of diisocyanate antigen-stimulated monocyte chemoattractant protein-1 (MCP-1) are more satisfactorily associated with OA to isocyanates than specific IgE and IgG.[5]

The aims of this study are therefore to describe the changes in immunological reactivity (specific IgE, specific IgG, MCP-1) in workers previously assessed at the time the diagnosis of diisocyanate-induced OA was made and who left further exposure to the agent after the diagnosis. We also compared the functional and inflammatory changes with immunological changes in the same workers.

Twenty-one subjects with positive specific inhalation challenges to isocyanates, 10 of whom were included at the time of diagnosis in our initial study but not in any

TABLE I. MCP-1, specific IgE, and specific IgG results at the time of diagnosis and follow-up*

	Diagnosis (baseline)					
	MCP-1 (n = 15)		Specific IgE (n = 21)		Specific IgG (n = 21)	
Follow-up	Positive	Negative	Positive	Negative	Positive	Negative
Positive	6	2	0 (3)	0 (0)	11	0
Negative	6	1	2 (5)	19 (13)	3	7
Total	12	3	2 (8)	19 (13)	14	7
Percent of total	80%	20%	10% (38%)	90% (62%)	67%	33%

*MCP-1 and antibody results are shown as positive if a positive result was obtained for any diisocyanate antigen tested (HDI, MDI, TDI). Specific IgE were assessed in 2 ways: an ELISA procedure using biotinylated goat antihuman IgE, followed by straptavidin-alkaline phosphatase, and an indirect/antiglobulin ELISA method (results in parentheses; see text). No statistical differences in the distribution of each parameter (MCP-1, specific IgE, specific IgG) from diagnosis to follow-up by the McNemar χ^2 test with continuity correction.

follow-up study,[5] and who stopped being exposed for 6.5 to 104 months were reassessed for clinical, functional, inflammatory, and immunologic (specific IgE, specific IgG, and MCP-1) outcomes at least 6 months after the first assessment, at a time that asthma was well controlled. The assessment included spirometry (FEV_1, forced vital capacity), airway responsiveness to methacholine, and examination of induced sputum.[6]

Serum specific IgG and IgE antibodies in plasma were assayed in triplicate by indirect ELISA.[5] IgE antibodies were also assayed by the biotin-spratavidin ELISA procedure.[7] Diisocyanate antigens were prepared by conjugation of hexamethylene diisocyanate (HDI), methylene diphenyldiisocyanate (MDI), and toluene diisocyanate (TDI) to HSA. Blood samples (60-100 mL) were collected for MCP-1 assessment and shipped overnight from Montreal to the University of Cincinnati Allergy Laboratory. Details of this methodology have previously been published.[5]

Antibody turnover rates in subjects producing antibody were estimated from the ELISA absorbance values for matched sera obtained at diagnosis and at follow-up, with both serum samples from individual subjects tested on the same ELISA plate. The rate constant (μ) for change in absorbance ($OD_{405\ nm}$) with time (t) caused by antibody levels was determined from the formula $ln\ OD_t = \mu t + ln\ OD_{t0}$. The rate of change was converted to the half-life ($T_{1/2}$) or the doubling time (T_D) for subjects showing decreasing or increasing antibody levels, respectively, calculated as $ln\ 2/\mu$.

The protocol was accepted by the Research Ethics Committee of Hôpital du Sacré-Coeur de Montréal, and all participants gave written consent to participate.

A test was considered positive for diisocyanate-specific antibody if the mean OD of triplicates was at least 0.1 and 3 SDs above the mean of 8 negative control sera. A test was considered positive if the maximal antigen stimulation of MCP-1 was 2 or more SDs above the mean MCP-1 amount quantitated in cell culture supernatant of a group of volunteers without asthma with no diisocyanate exposure.

Twelve subjects had OA caused by HDI, 4 each to MDI and TDI, and 1 to polyisocyanate. The interval between diagnosis and follow-up was 21 ± 24 months (all ≥6 months). At follow-up, 12 subjects were on inhaled steroids. Although FEV_1 (% predicted) was unchanged at follow-up (88% ± 17%) versus baseline (89% ± 20%), PC_{20} improved by ≥2-fold in 12 subjects. Of the 15 subjects who produced a satisfactory sputum sample, 4 had eosinophils ≥1% and 5 had neutrophils ≥60% (including 2 of the 5 subjects with sputum eosinophils ≥1%). Table I shows the results of MCP-1, specific IgE and IgG at the time of diagnosis and of follow-up visits. MCP-1 values (assessed in 15 of the 21 subjects) remained negative or positive at the follow-up visit in 7 subjects. In 6 other subjects, MCP-1 became negative, whereas it changed from negative to positive in 2 subjects. In contrast, specific IgE changed from positive to negative in 5 of the 8 indirect ELISA IgE positive subjects or in 2 of the 2 subjects positive by biotin-streptavidin IgE assay. In only 3 subjects did specific IgG change from positive to negative. The absorbance readings (concentration measurement) for specific IgG significantly diminished from baseline to follow-up visits in 10 of 14 (71%) of the subjects testing positive for IgG antibody from a mean (±SD) value of 0.36 (±0.19) to 0.14 (±0.11; $P = .005$) for any diisocyanate antigen and from 0.32 (±0.21) to 0.14 (±0.10; $P = .006$) for the workplace relevant antigen. The mean half-life of specific IgG antibodies to the work antigen was 2.3 years (minimum = 1.1 years; maximum = 6.4 years). There was no overall correspondence between the outcome of specific IgG in any specific subject (positive to positive, positive to negative, and so forth) and the outcome of MCP-1. There did not appear to be any relationship between antibody persistence and either duration of exposure, time away from exposure, or the diisocyanate chemical to which the subject was exposed.

We examined whether duration of exposure, duration of symptoms, FEV_1, PC_{20}, changes in FEV_1, changes in PC_{20}, and sputum eosinophils and neutrophils at the follow-up visit were different in subjects with positive and negative MCP-1, specific IgE and IgG results at baseline and follow-up visits (by unpaired *t* test or Kruskal-Wallis test in the case of sputum cells). No significant differences were found (Table II).

Diisocyanates are, with flour, the most common cause of OA.[8] Although many studies have been performed to elucidate the immunologic mechanism of isocyanate-induced asthma, the evidence is still controversial. There is, however, a consensus that increased specific IgE is highly specific, although not sensitive, for the disease.[3,9] Of the 21 subjects in our study, 8 (44%) had increased

TABLE II. Selected clinical, physiological, and inflammatory parameters in relation with the immunologic results†

	Baseline		Baseline		Baseline	
	Specific IgE		Specific IgG		MCP-1	
	Positive	Negative	Positive	Negative	Positive	Negative
	8	13	14	7	12	3
Duration of exposure (y)	15.0 (25.7)	15.8 (12.2)	14.4 (21.6)	16.9 (12.5)	9.1 (11.2)	10.9 (16.5)
Duration of symptoms (y)	4.8 (6.7)	4.1 (5.6)	4.0 (5.8)	4.9 (6.3)	4.3 (6.5)	1.2 (0.5)
FEV_1 (% predicted)	91.3 (18.4)	86.6 (16.7)	91.8 (16.8)	83.8 (17.3)	86.5 (13.2)	105.8 (26.2)
PC_{20} (mg/mL)	0.86	0.73	0.90	0.64	0.70	1.18
Changes in FEV_1 (% predicted) from baseline to follow-up	1.8 (12)	0.5 (14)	4.2 (10.8)	−3.0 (15.1)	−0.85 (15.6)	−0.69 (4.3)
Changes in PC_{20} (fold) from baseline to follow-up	9.4 (14.1)	5.5 (7.2)	7.2 (11.7)	6.3 (7.4)	7.8 (11.1)	0.4 (1.7)
Sputum eosinophils at follow-up						
n	4	11	8	7	10	2
(%) (median)	0.35	0.2	0.35	0.20	0.35	0.65
(25%-75% IQ)	(0.2-2)	(0.2-1)	(0.2-0.7)	(02-2.8)	(0.2-2.6)	(0.5-0.8)
Sputum neutrophils at follow-up						
n	4	11	8	7	10	2
(%) (median)	39.7	42.3	36.3*	63.7*	44.2	32
(25%-75% IQ)	(19-59)	(24-66)	(20-42)	(38-67)	(23-65)	(23-41)

IQ, Interquartile range.
**P* values between .1 and .05 for comparison.
†No significant differences by comparing subjects with positive and negative specific IgE, IgG, and MCP-1 at baseline (diagnosis) and follow-up visits by unpaired *t* test or, in the case of sputum cells, by Kruskal-Wallis test. PC_{20} results were transformed in logarithmic values for statistical analysis.

specific IgE at the time of diagnosis, which corresponds to the frequency of the presence of specific IgE antibodies in workers with OA to diisocyanates by the indirect ELISA method.[8] The prevalence of elevated specific IgE was lower with the biotin-avidin ELISA method used in our study (ie, using biotinylated goat antihuman IgE). The different results suggest that the indirect ELISA is either a more sensitive method or produces some false-positive reactions, possibly because of reaction to the enzyme labeled antirabbit IgG antibody with some human IgG antibodies.

Our work shows that the majority of workers with specific IgE antibodies at the time of diagnosis (5/8 or 62% and 2/2 or 100% depending on the methods used in our study) develops a negative test after being removed from exposure. This favorable outcome corresponds with what has been described for high-molecular-weight agents,[1,10] anhydrides,[2] and other studies of isocyanates.[3,4,11] In the report by Park et al,[4] high levels of specific IgE that were detected in 5 of 6 workers at the time of diagnosis declined to normal after a maximum interval of approximately 3 years away from work. Specific IgG antibodies to isocyanates have been found to be more sensitive but less specific than IgE antibodies in confirming OA. In our study, more workers had specific IgG antibodies (n = 14/21 or 67%) by comparison with specific IgE antibodies (n = 8/21 or 44% and 2/21 or 10% by the 2 methods used) at the time of diagnosis. Interestingly, specific IgG persisted in all but 3 subjects after removal from exposure, although the levels diminished significantly ($P = .005$) in 10 of 14 (71%) of the IgG-positive subjects. The half-life of specific IgG to isocyanates has been found to be longer than for specific IgE.[4] First, these results suggest that both cessation of exposure and loss of sensitization may play a role in the diminution of the level of specific IgG antibodies in workers exposed to diisocyanates. Second, if specific IgG plays the role of blocking antibodies, it may suggest that this defence mechanism persists for a significant duration (the mean duration of our study was almost 3 years) after removal from exposure. MCP-1 has only been recently proposed as a useful and valid test in the confirmation of OA caused by diisocyanates, with better sensitivity and specificity than specific IgE and IgG assessments as assessed in a sample of 54 workers exposed to isocyanates (19 with occupational asthma, 36 without) and 21 controls, including 12 with nonoccupational asthma.[5] Although MCP-1 became negative in 6 of 12 subjects, results went from negative to positive in 2 others. However, the heretofore unrecognized persistence and/or development of MCP-1 response of subjects long after cessation of exposure suggests a role for immunologic memory. There were no significant differences in several characteristics relevant to the persistence of the disease in subjects with OA (duration of exposure with symptoms, FEV_1, PC_{20}, and so forth) in subjects with presence or absence of specific IgE or IgG antibodies or MCP-1 at the time of diagnosis and follow-up. This is not a surprise, because clinical and functional outcomes are not generally paralleled by immunological changes in asthma. Outcome of immunological parameters should therefore not be taken as surrogates of clinical and functional outcomes. The majority of subjects (12/21, 57%) were on inhaled steroids, which can improve functional outcomes but are unlikely to influence immunological parameters. The duration of the follow-up was relatively short (nearly

TABLE II. (continued)

Follow-up		Follow-up		Follow-up	
Specific IgE		Specific IgG		MCP-1	
Positive	Negative	Positive	Negative	Positive	Negative
3	18	11	10	8	7
14.0 (18.1)	15.7 (18.4)	17.8 (23.4)	12.9 (9.5)	10.9 (13.7)	7.9 (9.9)
5.8 (7.1)	4.2 (5.8)	4.1 (5.9)	4.7 (6.1)	3.4 (4.5)	4.0 (7.5)
91.1 (10.1)	88.0 (18.2)	90.3 (20.6)	86.3 (13.0)	97.7* (18.0)	82.0* (12.8)
0.80	0.77	0.89	0.67	0.73	0.81
−1.5 (23.6)	1.3 (12.4)	1.7 (12.7)	0.2 (14.1)	−6.2 (15.3)	3.8 (11.0)
9.6 (5.3)	6.5 (10.2)	4.7 (7.7)	8.9 (11.5)	9.3 (14.0)	3.3 (5.1)
2	13	7	8	6	6
0.2	0.5	0.2	0.6	0.9	0.35
(0.2-0.3)	(0.2-1.8)	(0.2-0.5)	(0-2.7)	(0.2-1.4)	(0.2-3.6)
2	13	7	8	6	6
38.3	41	34	46	41	43
(12-64)	(29-65)	(19-64)	(38-65)	(20-64)	(23-65)

3 years, with the maximum interval 68 months). It would be interesting to know more about the changes over the course of time by re-examining our subjects in a larger group of subjects in a multicenter study at a later interval after discontinuing exposure, thus allowing for a more detailed description of the curve of changes as proposed in other studies.[1,2]

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Child-care center sandpits: A source of cat allergen (Fel d 1)

To the Editor:

The major cat allergen, Fel d 1, is distributed ubiquitously in the environment. Although most exposures of interest are in the home environment, it is also recognized that child-care centers are an important source of exposure to Fel d 1. For example, in a recent study in North