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Clinical aspects of allergic disease

Occupational asthma caused by tetrachlorophthalic anhydride: A 12-year follow-up

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Most patients with occupational asthma do not recover completely, even after several years away from exposure. Two case series, snow crab–induced asthma[1] and tetrachlorophalic anhydride (TCPA)-induced asthma,[2] have detailed information on changes in specific antibody level as well as on symptoms, lung function, and bronchial responsiveness. We report a 12-year follow-up of the TCPA asthma series.

A factory making electronic components introduced TCPA as an epoxy resin–curing agent in 1979, and in 1979 to 1980 it caused asthma in seven female workers. We confirmed the diagnosis by inhalation challenge, skin prick test, and specific IgE tests. They left the factory in 1980. Symptoms improved initially but then remained unchanged. Specific anti-TCPA IgE fell slowly up to 1984, with a half-life of 1 year.[2]

METHODS

The six living women (one died in 1981) were studied every 6 months after diagnosis until December 1982 and then in 1984, 1985, 1988, and 1992. A standardized questionnaire was used from 1984 on symptoms, medication, and smoking.

Abbreviations used

amp%max:	Amplitude (of daily PEF) expressed as a percentage of the daily maximum PEF
HSA:	Human serum albumin
PEF:	Peak expiratory flow
TCPA:	Tetrachlorophthalic anhydride

FEV_1 was measured with a Vitalograph spirometer (Vitalograph Ltd., Buckingham, England). In 1985 and 1988, bronchial responsiveness to histamine was measured with the method of Cockcroft et al.[3] and in 1992 measured with the rapid method of Yan et al.[4] Peak expiratory flow (PEF) variability was measured in 1985 and 1992 by recording the best of three blows on a Wright mini PEF meter six times per day for 28 consecutive days. The amplitude (difference between the maximum and the minimum PEF) was divided by the maximum PEF (amp%max) for each day, and the mean for the 28-day period was calculated.

Serum IgE binding to human serum albumin (HSA) control and TCPA-HSA conjugate was measured by RAST as previously described.[2] Values from 1980 to 1992 were plotted against time since last exposure and decay examined by SAS (SAS Institute Inc., Cary, N.C.). Skin prick tests were with 1% HSA control and 1% TCPA-HSA, and mean wheal diameter was noted after 10 minutes.

RESULTS

From 1984 to 1992 there was no trend for improvement in symptoms, bronchial responsiveness, or PEF variability or for decreased use of inhaled corticosteroids (Table I). TCPA-HSA skin prick tests, which had been positive in all tested subjects until 1988, remained posi-

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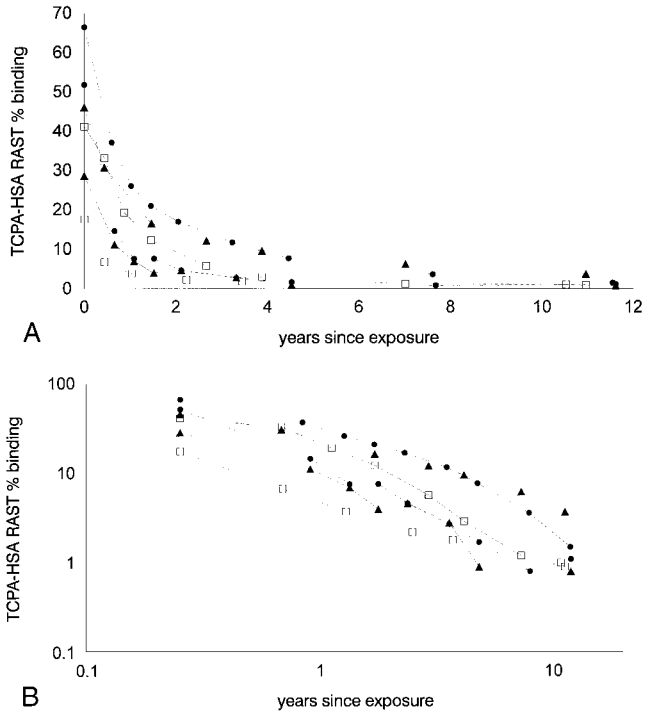

FIG. 1. A, TCPA-HSA–specific IgE against time plotted on linear scales; **B,** TCPA-HSA–specific IgE against time plotted on $\log_{10}$ scales. Serum from subject 6 has been diluted 1:5. For the $\log_{10}$ plot 3 months have been added to each time value to include time 0.

TABLE I. Symptoms and physiological data 1984-1992

Subject no. (age at diagnosis)	Year	Frequency of symptoms	FEV_1	Bronchial responsiveness to histamine 1985 and 1988 Cockcroft 1992 Yan (converted)	Peak expiratory flow variability (amp%max)	Inhaled corticosteroid per day beclomethasone (μg)	TCPA-HSA skin wheal size (mm)	TCPA-HSA RAST % binding - HSA
1 (34)	1984	daily	2.42	–	–	nil	4.5	5.1
	1985	daily	2.55	12.5	16%	nil	8.5	2.9
	1988	daily	2.60	16	–	600	2.0	1.2
	1992	daily	2.18	1.7 (5.9)	18%	600	3.5	0.8
2 (31)	1984	weekly	2.22	–	–	nil	2.0	2.1
	1985	weekly	2.16	3.1	–	400	2.0	1.8
	1988	daily	2.42	9.0	–	400	3.0	–
	1992	daily	2.45	2.9 (10.2)	20%	400	0.0	0.2
3 (40)	1984	weekly	1.92	–	–	nil	6.0	10.6
	1985	weekly	1.99	4.1	9%	400	7.5	9.3
	1988	weekly	2.17	7.8	–	400	5.5	6.7
	1992	weekly	2.00	0.3 (1.0)	18%	1000	11	3.8
5 (40)	1984	daily	2.20	–	–	nil	4.5	2.2
	1985	daily	2.19	2.7	16%	nil	1.5	1.8
	1988	monthly	2.01	1.8	–	nil	1.0	0.6
	1992	daily	1.79	0.8 (2.8)	27%	nil	0.0	1.0
6 (40)	1985	monthly	1.93	4.9	14%	nil	5.0	20.3
	1988	monthly	1.96	1.4	–	nil	5.0	11.0
	1992	daily	2.10	0.2 (0.8)	28%	400	6.0	7.6
7 (42)	1984	–	1.97	–	–	nil	6.0	2.8
	1985	–	–	–	7%	nil	–	–
	1988	weekly	1.90	1.2	–	400	–	1.0
	1992	weekly	1.96	3.7 (13)	12%	400	–	0.9

*Results from Cockcroft and Yan methods are expressed in mg/ml and μmol of histamine, respectively. Conversion in brackets is obtained by multiplying the result from the Yan method by 1.75 doubling increments.[8]

tive in three of five tested in 1992. Only two women were smokers in 1992.

TCPA-HSA–specific IgE continued to fall. The log-linear model used for 1980 to 1984[2] no longer described the data adequately because the half-life for IgE lengthened with time (Fig. 1). A log-log model was fitted that had been used to describe the decay of antihepatitis B antibody after active immunization.[5] Analysis of covariance had shown that the slopes for individual patients were not significantly different in the 1980 to 1984 data[2] but now indicated a statistically significant difference between patients. To calculate the half-life of specific IgE at intervals after last exposure to TCPA, we fitted a model with a common slope:

$$\text{Log}_e\ \%\ \text{binding} = -0.94\ \text{log}_e\ \text{time (years)} + \text{constant}\ (r^2 = 0.94).$$

This model would predict that 6 months after cessation of exposure, it would take a further 6.60 months (confidence interval [CI] 5.88, 7.44) for specific IgE to halve, whereas 8 years after cessation of exposure, it would take a further 8.74 years (CI 7.77, 9.96) for specific IgE to halve.

DISCUSSION

Six women, sensitized to a low-molecular-weight chemical to which they were exposed for less than 18 months in 1979 to 1980, have continued to have respiratory symptoms and bronchial hyperresponsiveness despite avoidance of exposure for 12 years and a progressive fall in specific IgE.

One other study, a 5-year follow-up of snow crab processing workers, has reported changes in specific IgE in association with symptoms, FEV_1, and bronchial responsiveness after avoidance of exposure. Bronchial responsiveness improved in the initial 2 years after leaving, but no further improvement occurred between years 2 and 5.[1] Over the same period, crab-specific IgE fell in a log-linear fashion, with a half-life of approximately 20 months.

The explanation for persistent symptoms and bronchial hyperresponsiveness is not known. Continuing environmental exposure to TCPA is unlikely because the patients left the factory in 1980 and the factory closed down a few years later. TCPA may remain bound to tissue, but there are no data on long-term hapten retention to support this. One possibility is that airway inflammation is maintained in the long term by autoantibodies directed at completely different epitopes in the airway mucosa.[6] Alternatively, after the initial immunologic insult, bronchial hyperresponsiveness might be maintained in the absence of an immunologic stimulus in some way analogous to reactive airways dysfunction syndrome.

The continuing antibody production implied by the persistent specific IgE response does not necessarily imply persistence of antigen. Studies on dogs subjected to localized lung immunization with a protein antigen showed that antibody production continued for at least 2 years after the last antigen exposure.[7] Furthermore, human anti–hepatitis B antigen titer falls 10-fold with every 10-fold increase in time after immunization with hepatitis B surface antigen,[5] a rate similar to that for anti–TCPA-HSA IgE.

Whatever the mechanism, these findings have implications for asthma where no current initiating cause can be identified: asthma and bronchial hyperresponsiveness may persist for at least a decade after the last exposure to the cause.

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