Occupational asthma in electronics workers caused by colophony fumes: follow-up of affected workers

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ABSTRACT Thirty-nine electronics workers were investigated by bronchial provocation testing to soldering fluxes containing colophony and were followed up one to four years later. At presentation and on follow-up each worker had nonspecific bronchial reactivity measured with inhaled histamine, and also had detailed measurements of lung function and estimation of total immunoglobulin levels. They completed a questionnaire designed to detect residual disability. The workers were divided into three groups. Twenty had left work after their initial diagnosis, eight had been moved to alternative work within their original factories, and 11 were thought to have asthma unrelated to colophony exposure as they failed to react to colophony at presentation. Histamine reactivity had returned to normal in half the workers who had left their original factories, but in only one worker who had moved within her original factory. This suggested that the nonspecific bronchial reactivity to histamine was the result rather than the cause of the occupational asthma, and that indirect exposure at work was sufficient to delay recovery of histamine reactivity. However, only two of the 20 affected workers who had left their original factories were symptom free on follow-up, and most had a considerable reduction in their quality of life by continuing asthma, which was particularly provoked by exercise, respiratory infections, and nonspecific irritants. Continuing symptoms may have been caused by domestic sources of colophony, or possibly the failure to eliminate colophony from the lungs.

Occupational asthma is usually caused by exposure to a single agent, from which a worker can be removed. It is often assumed that removal from exposure results in a cure of the asthma, although there is little documentation of this. It is difficult to provide objective data to measure disability from asthma. Infrequent lung function testing is generally unhelpful, and is often normal in workers with occupational asthma when measured during a day away from work.¹ The hallmark of asthma is variable airways obstruction; episodes of obstruction may be triggered by specific extrinsic allergens (such as occupational allergens) and by nonspecific stimuli such as exercise, cold air, and respiratory infections. Asthma induced by these nonspecific stimuli may be severe enough to limit seriously the quality of life.

The aims of this study were to reinvestigate a group of electronics workers who had been investigated at least a year earlier. All had had bronchial provocation testing to histamine as well to the fumes of soldering fluxes containing colophony during their initial assessment. Disability was assessed by a

questionnaire, supported by measurement of lung function, immunoglobulins, and nonspecific bronchial hyperreactivity to inhaled histamine. This was done before leaving work and on follow-up.

Methods

Forty-five electronics workers who had had provocation testing with colophony and histamine during their initial assessment were asked to attend for review. They included 31 who had occupational asthma caused by colophony fumes, as judged by a relevant history and a positive provocation test, and 14 who had negative colophony provocation tests.² Six workers were lost to follow-up. At presentation and on follow-up, each worker had detailed lung function testing and measurement of total immunoglobulins as already described.^{1,2} Bronchial reactivity to histamine was measured by the method of de Vries.³ All tests were started between 930 am and 1130 am, bronchodilators being withdrawn on the day of assessment. Thirty second inhalations of doubling concentrations of histamine acid phosphate were given, starting at 0.25 mg/ml and finish-

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ing at 32 mg/ml if no reactions had occurred by then. The histamine was nebulised in a Wright's nebuliser driven by oxygen at 8 litres/min and inhaled via a tightly fitting mask with a re-breathing bag. FEV₁ and FVC were measured on a dry-wedge spirometer (Vitalograph, Buckingham, England) until stable before testing and then five minutes after each dose of histamine. The test was stopped when the FEV₁ fell by 20% from its baseline value. Over short periods of time the test is reproducible within one concentration change, but a change to or from no reaction is always regarded as significant.

Each worker completed a standard questionnaire based on the 1976 MRC respiratory questionnaire with additional questions designed to detect intermittent disability and nonspecific factors provoking asthma. It also repeated the original questions used to diagnose work-related respiratory disease during epidemiological surveys in electronics factories,^{4,6} and ended with leading questions asking whether the worker had improved since moving work, or had reached his state of health before occupational asthma started.

After their initial assessment, the 31 workers with positive bronchial provocation tests to colophony fumes had been advised to change their place of work so that they were no longer exposed to colophony fumes. Nine were found alternative work within their original factories (called the group 2 cases) and 22 left work (called the group 1 cases). These two groups have been analysed separately, as those still working in electronics factories might have sufficient incidental exposure to colophony fumes to cause persisting symptoms. Fourteen workers who had negative provocation tests to colophony formed the control group.

Results

The details of the workers investigated are shown in table 1. Altogether 39 out of a possible 45 were followed up after a mean period of just over two years (range 12–45 months). Only seven of 20 of group 1 cases (who left their original employment) were re-employed, compared with eight out of eight group 2 cases (who had moved within their original factories), and nine of 11 of the controls. Two cases and one control had become symptom free. The details of breathlessness and wheeze are shown in tables 2 and 3. Twenty-one of 28 of the cases had a variable breathless grade between their best and worst days in the preceding three months compared with five out of 11 controls. Wheeze or breathlessness with weekend improvement occurred in one of 20 group 1 cases, eight of eight group 2 cases, and five of 11 controls. Nocturnal asthma was most common in those who had left work. Wheeze provoked by nonspecific factors such as exercise, cigarette smoke, paint fumes, hairsprays, and car exhaust fumes were common in all groups. Exercise asthma was a particular problem when carrying shopping. Twelve of 20 group 1 cases could no longer do their shopping on their own, compared with one of eight group 2 cases, and three of 11 controls. Only five workers were unable to do their housework on their own, distributed evenly between the three groups. All group 1 cases, five of eight group 2 cases, and two of 11 controls thought that they had improved since their initial assessment. Four out of 20 group 1 cases and no group 2 cases thought that they had returned to their state of health before occupational asthma started. Four of 11 controls thought that their presenting symptoms

Table 1 Details of the follow-up population: group 1 cases had left their original factories on follow-up, group 2 cases were re-employed in alternative employment in their original factories

	At presentation		
	Colophony challenge positive cases		Colophony challenge negative (controls)
	Group 1	Group 2	
Number in group	22	9	14
Number seen	20 (91%)	8 (89%)	11 (79%)
Women seen	19	7	10
Age—mean and range	52 (43–59)	45 (27–58)	47 (25–62)
Duration of follow-up (m)	29±1.9	27±2.9	23±3.2
mean ± SEM (range)	(16–45)	(13–40)	(12–41)
Smoking status at follow-up			
Current smokers	7	0	4
Exsmokers	3	2	1
Lifelong nonsmokers	10	6	6
Duration of symptoms before leaving work (m)	30±6.6	—	—
mean ± SEM (range)	(10–108)		
At work on follow-up	7/20 (35%)	8/8 (100%)	9/11 (82%)

Table 2 *Breathless grade on worst day in the last three months, and differences from the best day in the last three months*

	Challenge positive cases		Controls
	Group 1	Group 2	
Number seen	20	8	11
Not breathless (grade 0)	2	1	2
Breathless hurrying on flat (1)	3	0	4
Breathless walking on flat (2)	2	4	5
Stopping for breath on flat (3)	13	3	0
Difference between best and worst breathless grade in last 3 months	0 5 1 11 2 3 3 1	2 3 3 3 3 3 0	6 3 2 2 3 2 0

Table 3 *Occurrence of wheeze on follow-up*

	Challenge positive cases		Controls
	Group 1	Group 2	
Number seen	20	8	11
Night wheeze, at least twice per week	9	1	0
at least weekly	4	2	3
less than weekly	3	2	1
never	4	3	7
Daytime wheeze in last 3 mths	18	8	9
Nonspecific provocation of wheeze			
Cigarette smoke	9	4	6
Paint fumes	13	6	7
Hairspray	8	4	2
Car exhaust	6	5	2
Exercise	15	7	9

had resolved. Four of 20 group 1 cases, one of eight group 2 cases, and five of 11 group 3 cases were taking no treatment for their chest. The details of treatment being taken at follow-up is shown in table 4.

The results of lung function testing at presentation and on follow-up are shown in table 5. There were no significant differences for any group. The transfer coefficient for carbon monoxide (KCO), the mean value of which was low at presentation, was similarly low on follow-up.

The figure shows the threshold dose of histamine required to reduce the FEV₁ by 20% at presentation and on follow-up. Six of 20 group 1 cases had increased reactivity at presentation, which had returned to normal in nine at follow-up. A further two showed significant improvement. Five were not significantly changed. Six group 2 cases were abnormally reactive at presentation, only one of these had returned to normal at follow-up, and one had deteriorated significantly. The controls contained only three workers who were abnormally reactive at presentation; of these one was better, one the same, and one worse on follow-up.

The results of total immunoglobulins are shown in

Table 4 *Treatment being taken at follow-up*

	Group 1 cases n=20	Group 2 cases n=8	Controls n=11
Bronchodilator	15	7	4
Corticosteroids	9	3	1
Sodium cromoglycate	6	2	0
None	4	1	5

table 6. There was no significant change on follow-up in any group. The total IgM levels which were raised at presentation were similarly raised on follow-up.

Discussion

There are few follow-up studies of workers with occupational asthma. Chan Yeung⁷ followed a group of 38 workers with asthma caused by Western Red Cedar. Seventy-one per cent became asymptomatic when assessed an average of 1.5 years after leaving work. She thought that workers removed shortly after developing symptoms were more likely to become asymptomatic than workers who remained exposed for longer after symptoms developed. Adams⁸ followed 46 workers with symptoms related to toluene di-isocyanate more than six months after stopping exposure. Only six were asymptomatic compared with 18 of 46 controls. The affected workers also had reduced values for FEV₁ and FVC more than two years later. The only other follow-up study is in workers who had very high exposures to the enzyme alcalase in biological detergents.⁹ No distinction was made between sensitised and non-sensitised workers. The 13 most heavily exposed workers showed loss of elastic pulmonary recoil compared with 42 less heavily exposed workers when measured three years after the alcalase process had been stopped.

The present study was of selected workers who had been investigated by bronchial provocation testing in hospital. All workers, including the controls, were symptomatic on initial assessment. The final diagnosis in the controls was asthma unrelated to colophony exposure. It is very unlikely that the controls were missed cases of colophony asthma, as 82% were still exposed to colophony fumes, and only one had deteriorated in any parameter measured. Most controls were still symptomatic on follow-up, reflecting the disease present on initial assessment. There is evidence that the group with occupational asthma who had left work were more severely affected at presentation than those who moved within their original factory. This approach had been tried in some group 1 workers before they left work. Although all group 1 workers thought that

Table 5 Lung function expressed as percent predicted at presentation and on follow-up (means $\pm$ SEM)

	Challenge positive—no longer exposed				Challenge positive—still with some exposure				Challenge negative			
	First lung function		Follow-up lung function		First lung function		Follow-up lung function		First lung function		Follow-up lung function	
FEV ₁ % predicted	89.8 $\pm$ 4.9		86.3 $\pm$ 4.9		72.8 $\pm$ 12.7		74.8 $\pm$ 5.5		90.1 $\pm$ 11		84.5 $\pm$ 6.6	
FVC % predicted	100.3 $\pm$ 3.2		100.8 $\pm$ 3.4		80.6 $\pm$ 11.2		95.2 $\pm$ 10		96.1 $\pm$ 7.3		93.9 $\pm$ 4.8	
FEV ₁ /FVC—difference from predicted	-9.1 $\pm$ 2.3		-11.9 $\pm$ 2.4		-9.6 $\pm$ 6.2		-15.4 $\pm$ 3		-7.4 $\pm$ 5.4		+0.6 $\pm$ 10.5	
Total lung capacity (TLC) % predicted	105.5 $\pm$ 3		107.1 $\pm$ 2.8		104.2 $\pm$ 3.5		105.2 $\pm$ 6.2		101.3 $\pm$ 3.5		105.5 $\pm$ 3.6	
Residual volume (RV) % predicted	110.5 $\pm$ 7.5		124.6 $\pm$ 5.7		124.0 $\pm$ 12.2		125.0 $\pm$ 18.7		111.8 $\pm$ 10.7		120.6 $\pm$ 11.6	
Alveolar volume (VA) % predicted	100.0 $\pm$ 3.0		101.5 $\pm$ 2.6		85.8 $\pm$ 9.0		96.4 $\pm$ 4.9		92.7 $\pm$ 4.0		93.1 $\pm$ 3.6	
Tlco % predicted	90.8 $\pm$ 4.1		88.7 $\pm$ 4.4		92.6 $\pm$ 11.6		91.6 $\pm$ 7.2		88.5 $\pm$ 7.8		85.4 $\pm$ 5.5	
Kco % predicted	93.6 $\pm$ 3.4		90.2 $\pm$ 4.0		111.8 $\pm$ 8.8		98.4 $\pm$ 5.7		97.2 $\pm$ 5.8		94.7 $\pm$ 6.7	
FEV ₁ % predicted after bronchodilator	94.7 $\pm$ 4.2		93.3 $\pm$ 4.6		94.0 $\pm$ 9.4		94.6 $\pm$ 4.0		89.1 $\pm$ 10.1		89.8 $\pm$ 6.8	
FEV ₁ /FVC after bronchodilator—difference from predicted	-4.5 $\pm$ 2.1		-9.5 $\pm$ 2.3		-1.0 $\pm$ 4.9		-8.4 $\pm$ 2.3		+1.9 $\pm$ 13.1		-8.1 $\pm$ 4.3	
Air trapping (ml)	470.0 $\pm$ 77.5		627.0 $\pm$ 124.0		1390.0 $\pm$ 509.0		879.0 $\pm$ 312.0		697.0 $\pm$ 155.0		826.0 $\pm$ 171.0

Figure Threshold dose of histamine at presentation (1) and on follow-up (2) in three groups of electronics workers.

Table 6 Total immunoglobulin results at presentation and on follow-up (IU/ml means $\pm$ SEM)

	Group 1 cases		Group 2 cases		Controls	
	Presentation	Follow-up	Presentation	Follow-up	Presentation	Follow-up
Total IgG	145 $\pm$ 6.7	146 $\pm$ 6.2	164 $\pm$ 15	162 $\pm$ 12	139 $\pm$ 8	131 $\pm$ 9
IgA	143 $\pm$ 37	147 $\pm$ 21	132 $\pm$ 30	158 $\pm$ 30	136 $\pm$ 25	134 $\pm$ 22
IgM	224 $\pm$ 22	223 $\pm$ 24	284 $\pm$ 55	262 $\pm$ 37	221 $\pm$ 15	222 $\pm$ 18
IgE	135 $\pm$ 23	136 $\pm$ 22	137 $\pm$ 48	358 $\pm$ 217	165 $\pm$ 35	178 $\pm$ 49

they had improved since stopping colophony exposure, only two were asymptomatic. The group were predominantly middle-aged women, who often have some breathlessness as measured by the MRC questionnaire, but 13 of 20 had to stop for breath when walking at their own pace on level ground. This was often because even quite minor exercise induced their asthma. The exercise asthma was often provoked by shopping, such that 12 of them now required help with this. Respiratory infection frequently provoked quite severe asthma with nocturnal waking, neither of which had occurred with respiratory infections before their occupational asthma developed. Cigarette smoke,¹⁰ paint fumes, and hairsprays may each contain colophony. They are all common nonspecific causes of wheeze in patients with asthma and bronchitis. Only hairsprays were a less common provoker of wheeze in the controls compared with the affected workers.

There were no significant changes of detailed measurements of lung function between presentation and follow-up. Lung function was measured in the middle of the day when asthmatics are usually at their best. Single measurements of lung function are again confirmed as a poor method of assessing disability in asthma.

Extrinsic asthma to common environmental allergens requires both homocytotropic antibodies and nonspecific bronchial reactivity.¹¹ It is unclear how far occupational asthma resembles this model, particularly as IgE antibodies to small molecular weight industrial chemicals such as colophony are hard to identify. Total IgM antibodies are raised in electronics workers with occupational asthma, but are also raised in asymptomatic workers similarly exposed.^{5,6} IgM antibodies have no known role in releasing mediators from mast cells, but they were the immunoglobulins most commonly seen in the basement membranes of main stem asthmatic bronchi.¹² We have not found raised levels of IgM in workers with occupational asthma caused by isocyanates.

Increased bronchial reactivity to histamines has been found in many, but not all, workers with occupational asthma caused by colophony fumes. The hyperreactivity could have antedated colophony exposure or resulted from the sensitisation process. Bronchial reactivity returned to normal in more than half of those removed from exposure, suggesting that the hyperreactivity was the result of the sensitisation. This accords with the report of nine workers removed from Western Red Cedar exposure who showed improvement in methacholine reactivity on follow-up.¹³ Histamine reactivity returned to normal more frequently in those who had left work than in those who had moved within their orig-

inal factories, suggesting that the latter had sufficient indirect exposure to maintain their symptoms and bronchial reactivity. Although improvement was more noticeable in those who had left their original places of work, yet their morbidity was still considerable, despite many of them becoming unreactive to histamine. It is possible that they were still being exposed to sufficient colophony to maintain their symptoms. Possible sources of colophony include colophony brought home on the clothes of friends and relatives who were still working with colophony, domestic sources of colophony, and colophony inhaled at work which had not yet been eliminated. Two workers had husbands who worked in electronics factories who could have brought colophony back in their hair and clothes. Asthma on contact with exposed workers is a feature of highly sensitive subjects and potent allergens, and has been described in workers sensitised to antibiotics, platinum salts, and laboratory animals. The degree of sensitivity in the solderers was generally only moderate, and the eliciting concentration usually in the order of 0.5 mg/m³, as opposed to 0.002 mg/m³ for platinum salts, and probably even lower concentrations for the antibiotics and laboratory animals.

Colophony and pine products are still widespread in the home. Many domestic cleaners are "scented" with pine essence, and provoked symptoms in some workers. As previously mentioned, cigarettes,¹⁰ hairsprays, and paints may all contain colophony which could be inhaled. Most domestic sources such as sticking plasters, adhesives and insulating tapes are, however, in the solid state; these are unlikely to result in inhaled colophony. Pine trees and Christmas trees have both provoked asthma in affected workers and colophony has been detected in the air around pine trees (C Edmunds, personal communication).

Nothing is known of the fate of inhaled colophony. It is not water-soluble and is a reactive adhesive, making it likely that it would become firmly bound to tissue. It is at least possible that colophony may persist in the lungs for several years, causing low grade persistent symptoms. Indirect evidence for continuing exposure to colophony comes from the raised levels of IgM which were found in exposed workers. IgM antibodies usually fall when the antigen is eliminated. Their persistence suggests that either there is sufficient exposure to colophony to maintain antibody levels or that IgM antibodies are unrelated to colophony sensitisation.

It could be argued that the workers with occupational asthma were all going to develop late onset asthma, and that the occupational colophony exposure merely exacerbated this. Brostoff¹⁴ found an excess of homozygotes for BW6, a long arm antigen

on the HLA-B locus, in intrinsic asthmatics. HLA-BW6 homozygotes were not increased in this group, suggesting, with the return of histamine reactivity towards normal, that those sensitised had acquired a disease that they would have been spared had it not been for their job.

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