Occupational formalin asthma

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ABSTRACT Hypersensitivity to formalin used to sterilise artificial kidney machines was shown by inhalation provocation tests to be responsible for attacks of wheezing accompanied by productive cough in two members of the nursing staff of a haemodialysis unit. Three further members of the staff of 28 who were continually exposed to this substance occupationally had developed similar recurrent but less frequent episodes since joining the unit. Two underwent inhalation provocation tests with formalin which did not reproduce these symptoms. Single episodes of these symptoms had been noted by three additional staff members so that altogether eight (29%) had experienced attacks described as bronchitic since becoming exposed to formalin. We suggest that, while exposure to formalin did not seem to be directly responsible in all cases, it might have increased susceptibility to other provoking agents or induced a hyper-reactive responsiveness of the airways. The responses observed in the two nurses after inhalation provocation tests with formalin were predominantly of airways obstruction. Wheezing began between two and three hours after exposure, and peak expiratory flow rates fell maximally by approximately 50%. Reactions persisted for 10 hours to 10 days depending on the exposure dose. A productive cough was a prominent feature. The sputum appeared to be mucopurulent, but culture produced a scanty growth of *Haemophilus influenzae* only, together with upper respiratory tract commensals. The cellular content was not homogeneous, neutrophil leucocytes and eosinophil leucocytes variably dominating. Variable responses of neutrophil and eosinophil leucocytes were also seen in the peripheral blood.

Although contact dermatitis caused by formalin sensitivity is well recognised, the intrathoracic airways appear to be surprisingly immune to this toxic substance despite its immediate intense irritative effect on the eyes and upper respiratory tract. Both pneumonitis (Porter, 1975) and asthma (Sakula, 1975) have recently been reported after occupational exposure to formalin, and there are three previous reports of occupational asthma shown to be attributable to formalin sensitivity by inhalation provocation tests. Vaughan (1939) described a match factory worker with this disorder and Popa *et al.* (1969) reported a number of similarly affected workers engaged in the tanning and rubber industries. More recently we described a nursing sister from a renal haemodialysis unit who had developed asthma as a result of continual exposure to the formalin used to sterilise the artificial kidney machines (Hendrick and Lane, 1975). Since then another nurse from the same haemodialysis unit has been shown to be affected and this prompted a survey of all the members of the staff in an attempt

to assess the importance of formalin as a cause of occupational asthma. This paper reports the results of these investigations.

Materials and methods

THE HAEMODIALYSIS UNIT

From its foundation in 1967 until this study was completed early in 1976, the unit was housed in temporary, restricted, and poorly ventilated quarters. While most patients received treatment routinely in their own homes, two shifts of six patients were dialysed daily in the unit in a section measuring 7 × 10 m equipped with two small extractor fans. Immediately adjacent was an area measuring 7 × 7 m in which pumping machines and artificial kidneys were sterilised with formalin. Two further extractor fans were fitted to windows in this section. Both sections of the unit were of open-plan design, and formalin vapour was usually readily detectable throughout.

FORMALIN

All the Kiil artificial kidneys were sterilised with

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formalin as were some of the pumping machines, others being heat sterilised. The stock preparation was formalin BPC (34-38% solution of formaldehyde in water w/w) which was known as 100% formalin. Dilutions of 70% and 2% were prepared in the unit by the staff for the different sterilisation processes.

STAFF

There were 12 nurses, 10 nursing auxiliaries, and two domestic assistants who spent most of their working hours in the unit and were exposed continually in varying degrees to formalin. In addition four technicians were similarly exposed in the course of servicing formalinised equipment.

SURVEY

All the staff were interviewed and underwent simple tests of airways function, namely peak expiratory flow (PEF) using a Wright's meter, and one second forced expiratory volume (FEV₁), and forced vital capacity (FVC) using a Vitalograph dry spirometer. The results were compared with predicted values for normal subjects from Bates *et al.* (1971) and from nomograms supplied by Vitalograph Limited.

INHALATION PROVOCATION TESTS

Four staff members and a sister of one patient, all of whom had histories of recurrent attacks of wheezing since becoming exposed regularly to formalin, were invited to undergo inhalation provocation tests. All gave their informed consent. They had no respiratory symptoms, no respiratory medications, and no exposure to formalin for at least 24 hours before each test. After baseline tests of airways function, occupational exposure to formalin was simulated by formalin solutions of varying concentrations being painted by the subjects on the same piece of cardboard on different mornings within a specially designed challenge cabinet. Its dimensions were 1.0 × 1.4 × 2.1 m and the cardboard measured 0.4 × 0.4 m. A nose clip was worn throughout in the hope that tests with formalin would not be distinguished from control tests with water. The subjects were closely observed throughout the exposures, which could have been terminated immediately had there been undue discomfort. Ten minutes' painting consistently produced an uncomfortable atmospheric concentration of formalin vapour and so tests requiring longer exposures were generally interrupted at 10-minute intervals. Formalin vapour was extracted from the cabinet by a fan before each subsequent exposure so that similar quantities were inhaled during each period of 10 minutes. Peak expiratory flow rates (the best of three consecutive readings) were recorded at 10-minute intervals for one hour after each formalin exposure began, and

at hourly intervals while the subject was awake for the next 24 hours.

Blood was taken for haematological investigations immediately before and 24 hours after each test.

Results

SYMPTOMS

Five of the 28 staff members reported that recurrent episodes of productive cough accompanied by wheeze had developed for the first time since they had joined the unit and had continued for at least three years. Attacks generally occurred in winter and often followed colds. The five affected included the two nurses whose symptoms were shown to be attributable to formalin before the survey was carried out. Only these two had recognised a relationship between symptoms and exposure to formalin, but this recognition did not come until they had had attacks for about two years. Two of the five had never smoked, two were light smokers (fewer than 10 cigarettes daily) and one had smoked 15-20 cigarettes daily for 30 years. Their ages ranged from 32 years to 57 years (mean 45 years). Four underwent inhalation provocation tests with increasing exposures to formalin; these are described more fully below (Cases 1-4).

Three additional otherwise healthy staff members, who were all life-long non-smokers, had each suffered a single episode of productive cough with wheeze since joining the unit. Two had never previously experienced such symptoms and the third had had one previous episode 10 years before. Thus overall eight (29%) had been affected since becoming exposed occupationally to formalin.

One other nurse, who worked part-time on two consecutive days weekly, reported an intermittent dry cough. In general it started during the first of her two days each week, reached its most troublesome stage after her second day, and cleared up during the next two days. She had had the cough for three months and it was not getting worse. She had never smoked.

PULMONARY FUNCTION TESTS

All staff members were asymptomatic when these tests were carried out, and all readings of FEV₁, FVC, and PEF were close to predicted normal values. In all cases the ratio FEV₁/FVC exceeded 70%.

Case reports

CASE 1

A 41-year-old woman

This nursing sister began working in the dialysis unit

in 1969 at which time she had no respiratory symptoms. A dry cough developed within a few months which was at first episodic, then persistent. Soon after, she developed attacks of wheezing for the first time in her life. These occurred initially once every few months, were mild and lasted a few hours. She did not seek medical advice but did stop smoking (5-10 cigarettes daily for 10 years), which brought no relief. She recalled two attacks lasting between four and five hours which followed exposures of 5-20 minutes to spilled undiluted formalin, but there were no other obvious provoking factors. In 1973 after a cold she coughed up sputum which was mucopurulent, although no pathogens were isolated on culture, and her wheezing became continuous and distressing. She did not respond satisfactorily to bronchodilators or antibiotics and after two months was obliged to take sick leave. At this time a chest radiograph revealed inflammatory changes in the apical segment of the right lower lobe and her white blood cell (WBC) count was $13.1 \times 10^9/l$ of which $2.1 \times 10^9/l$ were eosinophils. Routine skin prick tests using 12 common allergens proved negative. She improved steadily but slowly and had fully recovered by the time the inhalation provocation tests were carried out one month later. By this time she was taking no medication and was back at work, although avoiding undue exposure to formalin.

Details of the inhalation provocation tests are given in Fig. 1. The nose clip did not prevent her recognising 100% formalin used in test 1, but did prevent recognition of 25% formalin used in subsequent tests. She noted no respiratory symptoms during any of the test exposures.

Test 1 consisting of 20 minutes' intermittent

exposure to 100% formalin over a 75-minute period produced a late asthmatic reaction. Wheezing started about three hours after initial exposure to formalin and reached its maximum intensity approximately six hours later. She was not unduly troubled and considered the reaction similar to the attacks she had experienced previously. Salbutamol by inhalation produced some subjective but little objective improvement in airways function, and she did not feel fully recovered for several days. Indeed, when test 2 was carried out nine days later, tests of airways function were still appreciably impaired, although by then she was without symptoms. In view of this prolonged reaction, 25% formalin was used in subsequent tests. Test 2 (5 minutes' exposure) produced no response, but after test 3 (15 minutes' exposure) there was a late asthmatic reaction of similar onset and intensity although of a shorter duration to that observed after test 1. Test 4 showed that the reaction to 15 minutes' exposure to 25% formalin could be inhibited by the earlier inhalation of betamethasone-17-valerate 200 μ g. After these tests there was no febrile response nor was there any significant haematological change in peripheral blood.

After these tests, more effective extractor fans were fitted to the dialysis unit and undiluted formalin was handled more carefully. In particular, she avoided unnecessary exposure and no longer cleared up spilled undiluted formalin herself. These simple measures enabled her to pursue her job with minimum inconvenience, and three years later she was still working in the unit. She was then free of wheeze, and tests of airways function were within the predicted normal range. A mild dry cough persisted, despite continued abstinence from smoking.

Fig. 1 Case 1: results of inhalation provocation tests.

20.7.73 (1000 h)	-----	Test 1	100% formalin	4 x 5 min.
29.7.73 (1000 h)	————	Test 2	25% formalin	5 min.
30.7.73 (0945 h)		Test 3	25% formalin	15 min.
31.7.73 (1115 h)	-----	Test 4	25% formalin	15 min.
21.8.73 (1100 h)		Control		

CASE 2

A 32-year-old woman

This nurse began working in the unit in 1972. She was then generally well, but had suffered classical hay fever since early childhood, and was aware that heavy exposures to house dust provoked immediate, short-lived attacks of wheezing. In addition mild wheezing usually accompanied common colds. She was a life-long non-smoker. Within six months she experienced her first attack of wheezing unrelated to house dust or to a common cold. Attacks increased in frequency and severity during the ensuing two to three years and she learned to associate them with relatively heavy exposures to concentrated formalin. Exposure to 70% formalin for 20 minutes would provoke an attack that started while she was still at work, worsened at home the following evening, and awoke her during the night when it reached its maximum intensity. A consistent feature was an early dry cough which became productive of mucopurulent sputum shortly before the onset of the wheezing and which persisted throughout the attack. She experienced 5-10 such episodes requiring on occasions between one and two weeks for full recovery. Between these more severe attacks she was relatively untroubled, although she occasionally noticed a mild wheeze. She did not take time from work and did not seek medical advice until the nursing sister (Case 1) observed an attack in late 1975, which led to her referral.

Investigations were carried out soon afterwards at which time she was without symptoms. A chest radiograph showed no abnormality. The white blood cell count was $16.1 \times 10^9/l$ of which $1.4 \times 10^9/l$ were eosinophils. Routine skin prick tests with 12

common allergens showed strong immediate reactions to grass pollen, house dust, and the house dust mite *Dermatophagoides pteronyssinus*.

The results of the inhalation provocation tests are given in Fig. 2. Despite the nose clip, she recognised formalin at both concentrations because the vapour irritated her throat, but there was no cough or chest discomfort during any of the test exposures.

Test 1 (8 minutes' exposure to 25% formalin) produced a late asthmatic reaction which started between two and three hours after the exposure to formalin began and reached a maximum approximately 22 hours later. She recognised it as similar to her previous attacks, and the cough, initially dry then productive of apparently mucopurulent sputum, again preceded the onset of wheezing. She did not become unduly distressed, despite PEF decreasing by more than 50% of pre-exposure values and was content for treatment to be withheld so that the full course of the reaction could be observed. Wheezing continued for eight days during which the degree of airways obstruction showed a marked diurnal variation (Fig. 3). No treatment was given and she remained off work and so free from further contact with formalin. Test 2 (5 minutes' exposure to 10% formalin) produced a reaction of similar onset and intensity despite the earlier inhalation of betamethasone 17-valerate 200 μg . It was responsive to salbutamol by inhalation, but this caused nausea and was discontinued. Twenty-four hours after exposure she felt fully recovered but during the following afternoon PEF began to decrease once more. She was treated with betamethasone 17-valerate 200 μg four to six hourly and her subsequent course was uneventful. After test 3 (repeat 5 minutes'

Fig. 2 Case 2: results of inhalation provocation tests.

14.11.75 (0945 h)	Test 1	25% formalin	8 min.
25.11.75 (1030 h)	Test 2	10% formalin	5 min.
4.12.75 (1030 h)	Test 3	10% formalin	5 min.
13.11.75 (0945 h)	Control	water	10 min.

Fig. 3 Case 2: diurnal variation of prolonged reaction.

exposure to 10% formalin) pulmonary function was monitored using a whole body plethysmograph in addition, initially at 5-10 minute intervals then half hourly. There was no significant change in specific airways conductance, FEV₁ or PEF for two hours, but all were reduced by similar proportions after 2½ hours. On this occasion she was electively treated with oral prednisolone, and had fully recovered the next day.

Blood was taken immediately before and 24 hours after the control test and tests 1 and 2. There was no significant change haematologically after the control test, but the total WBC rose from 13.6 to 17.9 × 10⁹/l after test 1 and from 12.2 to 16.0 × 10⁹/l after test 2. Neutrophils and lymphocytes were predominant in the response after test 1, whereas eosinophils and lymphocytes were chiefly responsible for the change after test 2.

The sputum was examined after one of the tests. Specimens were obtained 2½ hours and 24 hours after exposure to formalin began. They were mucopurulent but both yielded on culture a scanty growth of *Haemophilus influenzae* only, and normal upper respiratory tract commensals. The 2½-hour specimen contained many eosinophil leucocytes, often in clumps, but overall neutrophil leucocytes predominated. The 24-hour specimen showed no excess of eosinophil leucocytes.

She too returned to work, but avoided excessive exposure to formalin and when examined three months later had had no further attacks. She was then perfectly well, and tests of airways function showed no abnormality. A subsequent unavoidable moderate exposure to formalin led to a short-lived recurrence of symptoms, and soon after this she decided to change her occupation.

CASE 3

A 57-year-old woman

This nurse began working in the unit in 1967. Since 1972 she had suffered between one and five episodes of winter bronchitis each year. Sometimes these kept her from work for as long as 10 days. They comprised cough with mucoid sputum, wheeze and mild breathlessness, and generally followed colds. There was no obvious relationship with formalin. Between attacks she had no symptoms. In particular there was no cough, although she had smoked 5-10 cigarettes daily since 1940. She had not wheezed previously.

She underwent three inhalation provocation tests with increasing exposures to formalin which produced no reactions (Fig. 4). The exposure of test 3 (60 minutes' intermittent exposure to 25% formalin during an 85-minute period) was thought to have exceeded any she had encountered occupationally. Tests of airways function were within the normal predicted range and there was no haematological abnormality of peripheral blood either before or after any of these tests.

CASE 4

A 48-year-old man

This technician began working in the unit in 1967. Within two years he became aware that heavy exposures to formalin caused redness and weeping of the eyes coupled with a sensation of grittiness which could persist for several days. He subsequently developed attacks of bronchitis between one and three times each winter, with productive cough, wheeze and mild breathlessness which he felt were not related to formalin. Between attacks he was without respiratory symptoms. He had never smoked.

Fig. 4 Case 3: results of inhalation provocation tests.

17.12.75 (1015 h)	Test 1	10% formalin	5 min.
18.12.75 (1045 h)	Test 2	25% formalin	3 × 5 min.
20.12.75 (1000 h)	Test 3	25% formalin	6 × 10 min.
16.12.75 (1100 h)	Control	water	5 min.

He underwent two inhalation provocation test exposures of 5 and 20 minutes to 25% formalin. Neither produced any respiratory reaction, but a troublesome conjunctivitis occurred after each, despite in the case of the second test the use of a scuba diving mask throughout the exposure. Discomfort persisted for a number of days and so no further tests were carried out.

CASE 5

A 12-year-old girl

A patient who began regular home haemodialysis treatment in 1970, used to have her 12-year-old sister to provide company within the small Portakabin that housed the dialysis equipment on most evenings that treatment was received. At these times the sister was exposed to formalin vapour and in February 1975 she developed a cough with mucoid sputum, chest tightness, wheeze, and general malaise. Her progress was unsatisfactory and she was referred to a paediatrician who diagnosed asthma. A severe attack in August 1975 led to emergency hospital admission. Subsequent attacks, mostly provoked by exercise, were mild and responded well to salbutamol orally. She was unaware of any other obvious provoking factor although she realised that house dust provoked immediate sneezing. As soon as she became aware of these investigations another sister, who shared her bedroom, suggested that her wheezing was more pronounced during the night and morning after dialysis. Skin prick tests showed moderately strong reactions to house dust *Dermatophagoides pteronyssinus*, feathers, and dog hair. No venesections were performed because of her age.

No reactions were obtained to the three inhalation provocation tests with increasing exposures to formalin (Fig. 5). Test 3 (60 minutes' intermittent exposure to 25% formalin during an 85-minute period) was thought to have exceeded any exposure encountered naturally.

Discussion

The late asthmatic responses to inhaled formalin vapour demonstrated in the two nurses are essentially similar to those described in sensitised subjects after inhalation of a number of other relatively simple reactive chemicals. The best known is toluene di-isocyanate (Pepys *et al.*, 1972a), while other examples include aluminium soldering flux fumes (Sterling, 1967), platinum salts (Pepys *et al.*, 1972b), ampicillin and related antibiotics (Davies *et al.*, 1974), and epoxy-resin fumes (Fawcett *et al.*, 1976). It is a feature of chemically-induced asthma that reactions to single exposures may persist for several days, in some cases even for weeks. Both these nurses had sustained attacks in the course of their occupations which persisted for between one and two weeks and tests showed that airways function was still impaired 10 days after the first inhalation provocation tests. The duration of the response appeared to depend on the extent of the exposure. In both nurses exposure to lesser concentrations of formalin for shorter periods provoked reactions whose durations were greatly reduced, although they had begun after similar intervals and had reached similar intensities. Furthermore, in the case of the first nurse no reaction was detected until the exposure to 25% formalin was increased from 5 to 15 minutes,

Fig. 5 Case 5: results of inhalation provocation tests.

suggesting that there was a threshold level. This was paralleled by the clinical history of many working days spent without symptoms, both before and after these investigations were completed.

The marked diurnal variation to the prolonged reaction after test 1 in the second nurse is of particular interest and suggests an appreciable intrinsic component to this example of extrinsic asthma.

A response of this kind is not generally recognised, despite its original clear description firstly in Western red cedar workers (Gandevia and Milne, 1970) and then in enzyme detergent workers (Mitchell and Gandevia, 1971). More recently a further example was reported after exposure to grain dust in a farmer (Davies *et al.*, 1975).

The absence of any pulmonary reaction to the inhalation provocation tests in the other three subjects confirms that the responses demonstrated in the two nurses were not non-specific in nature. Fortunately these three, a smoker and a non-smoker with recurrent bronchitis and an atopic asthmatic, provide a good spectrum of controls. They may be augmented by our previous report (Hendrick and Lane, 1975) of a pathologist with atopic asthma in childhood succeeded by smoker's bronchitis who also failed to respond to inhalation provocation tests with finally 25% formalin for 60 minutes over an 85-minute period.

The mechanism underlying late reactions of this type is not clear. Where more complex organic allergens are involved, circulating precipitating antibodies are usually demonstrable and a type 3 hypersensitivity reaction (Gell and Coombs, 1968) has been suggested. Formaldehyde however is a relatively simple chemical and is commonly assumed to be non-antigenic. It is none the less a reactive

chemical and may exert its effects through immunological mechanisms acting as a hapten, but evidence that this is so is at present lacking. It is interesting that the second nurse was an atopic subject, who might consequently have been expected to show an immediate (type 1) as well as a late asthmatic reaction to formaldehyde if it was indeed acting in a comparable way to organic allergens. None was detected, however, despite the additional more sensitive measurement of specific airways conductance after test 3.

A further feature of late asthmatic reactions is the unpredictable, but often poor, response to sympathomimetic bronchodilators. Little response to inhaled salbutamol was seen in the first nurse, although the immediate effect in the second was more satisfactory. Corticosteroids are more effective and late reactions produced after provocation tests may generally be inhibited, either by a single pre-exposure dose or by doses repeated three to four hourly (Pepys *et al.*, 1974). The earlier administration of betamethasone-17-valerate 200 μ g by aerosol proved sufficient to inhibit the reaction in the first nurse to exposure to 25% formalin for 15 minutes, but did not modify the reaction in the second nurse to 10% formalin for five minutes. The results from the continued use of betamethasone aerosol and oral prednisolone after tests 2 and 3 suggest that corticosteroids were effective in the case of the second nurse also, provided repeated doses were used.

The expectoration of mucopurulent sputum by both affected nurses is a particularly interesting feature of these airways responses to inhaled formalin vapour. It increases the difficulty of distinguishing clinically between asthma and bronchitis and it illustrates that mucopurulent sputum may not

always be the consequence of active bacterial infection. Although the excess of eosinophil leucocytes in both sputum and peripheral blood supports the possibility that the underlying mechanism may be an allergic one, it is clear that neutrophil leucocytes were also prominent, and these may be the consequence of other processes.

Although the survey uncovered no further cases of occupational asthma that inhalation provocation tests could show were related to formalin, a surprisingly high proportion of the staff (eight out of 28: 29%) reported attacks of bronchitis (productive cough accompanied by wheeze) since starting work in the unit. In five of these eight, attacks had been recurrent for at least three years, and only one of the eight had ever experienced such symptoms before joining the unit, a single episode 10 years previously. None apart from the two nurses described in detail were able to relate attacks directly to particularly heavy exposure to formalin, and many thought that common colds were chiefly responsible. One was a moderate smoker, two were light smokers and the remaining five had never smoked, so that any part played by tobacco smoke was slight. The overall numbers are small and these findings may be accountable to chance alone. We suggest, however, that continual exposure to formalin vapour may increase susceptibility to attacks of bronchitis or induce a hyper-reactive responsiveness of the airways, so that some of the airways responses reported by the staff of this renal dialysis unit whether provoked immediately by common allergens infection, smoke, or other irritants might not have occurred were it not for the concomitant exposure to formalin. This suggestion is supported by one report of toluene di-isocyanate asthma in which Sweet (1968) noted that asthmatic responses were provoked by house dust and barn dust during convalescence from occupationally-induced isocyanate asthma, but not at other times. Alternatively, it could be the common cold that induced bronchial hyper-reactivity, a hypothesis recently advanced by Empey *et al.* (1976), and the coincident or convalescent exposure to formalin that directly provoked the bronchitic or asthmatic episodes.

Formalin asthma has not been reported in staff of renal haemodialysis units elsewhere, and there are only two reports of formalin-induced respiratory disease in workers in laboratories where this substance is also widely used (Porter, 1975; Sakula, 1975). It seems likely that its occurrence in this particular unit owes much to the relatively heavy exposures sustained as a result of restricted space and poor ventilation. Happily new permanent quarters were occupied shortly after the survey was completed and the working environment improved greatly.

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