

Correspondence

Non-specific bronchial hyperresponsiveness induced by occupational exposure to different irritants

SIR, Bronchial hyperresponsiveness to non-specific stimuli is a common feature of bronchial asthma, as it can be observed in most affected subjects [1]. Several studies have been carried out in an attempt to understand whether this phenomenon is a pre-existing inherited factor, predisposing to asthma, or rather a consequence of exposure to the sensitizing agent. An acute, reversible increase in NSBH, from a normal to an asthmatic range, has been observed in sensitized subjects after exposure to chemical agents [2,3]. In previously normal subjects a single heavy exposure to chemicals can also induce NSBH which may persist over several years even in the absence of further exposure to the agent responsible [4,5].

We report three cases in which NSBH was induced by occupational exposure to irritants not commonly considered to cause asthma.

Case reports

Patient 1: TF, a 25-yr-old male, was first seen in November 1985. His past health had been good, he had stopped smoking 1 yr ago, having previously smoked 20 cigarettes per day for 6 yr.

In 1982 he developed symptoms of sneezing, dry cough, chest tightness and wheezing, without any relationship with season, which could be relieved by bronchodilators. He worked as a shoe-maker and was exposed to the solvents and dyes for shoe soles for 8 yr, but he was not exposed to isocyanates or formaldehyde. His symptoms were worse on work days and when breathing cold air.

At presentation, FEV_1 was 3.56 l (85% of predicted value). A non-specific bronchial provocative test (nsBPT) was performed by the method previously described [6] using methacholine solution (0.4 and 4% w/v in phosphate-buffered solution). Increasing cumulative doses of methacholine (0.040–3.2 mg) were inhaled by means of a 646 DeVilbiss nebulizer connected to a dosimeter, until either a decrease of 30% in FEV_1 or a cumulative dose of 3.2 mg were reached. The provocative dose able to induce a 15% fall in FEV_1 ($PD_{15}FEV_1$) was calculated on a log dose–response curve, and a $PD_{15}FEV_1 \leq 1$ mg was considered as a marker of NSBH. The first nsBPT, performed when still at work, showed a severe NSBH ($PD_{15}FEV_1 = 0.054$ mg). He then performed several nsBPT, when still at work and after short periods of work cessation because of symptom worsening (Fig. 1a). Figure 1a shows that 3 weeks of work cessation were sufficient to improve pulmonary function ($FEV_1 = 4.13$ l; 98% of

predicted), even if NSBH was still present and severe ($PD_{15}FEV_1 = 0.086$ mg). After 5 weeks of temporary cessation of work, NSBH was considerably improved ($PD_{15}FEV_1 = 0.840$ mg). Two days after starting a new period of work exposure, $PD_{15}FEV_1$ decreased to 0.307 mg, and after a week of continuous exposure to occupational irritants NSBH worsened considerably ($PD_{15}FEV_1 = 0.060$ mg) and FEV_1 fell to 3.31 l (79% of predicted).

Patient 2: GA, a 39-yr-old male, was first seen in October 1985. His past health had been good and he had never smoked. Ten years earlier he had developed symptoms of mild dyspnea after physical exercise, and wheezing after viral infection of the airways, or when exposed to cold air or irritants such as cigarettes smoke or gases. Five years later, he developed symptoms of wheezy dyspnea, regardless of season. He had worked in a bus garage for 13 yr and was exposed to exhaust gases, soldering fumes and, occasionally to polyurethane varnish.

At presentation, FEV_1 was 3.16 l (73% of predicted). The first nsBPT, performed when still at work, elicited a $PD_{15}FEV_1$ methacholine of 0.040 mg. He also underwent a specific bronchial provocative test with toluene-diisocyanate, performed by exposure to toluene-diisocyanate vapours (20–60 p.p.b.) in a challenge chamber for 30 min [6], with a negative response. Then alternate periods of work and work cessation followed, during which he performed several nsBPT (Fig. 1b). Five days after cessation of occupational exposure, $PD_{15}FEV_1$ increased, thus falling within the range of normal subjects (1.6 mg), and FEV_1 also increased (3.34 l; 81% of predicted). He then started a new period of occupational exposure, with a progressive worsening of NSBH ($PD_{15}FEV_1 = 0.24$ mg, after 5 weeks).

Patient 3: FD, a 27-yr-old female, was first seen in September 1985. Her past health had been good. She had been smoking 10 cigarettes per day for 11 yr.

About 5 months before the first examination, she developed symptoms of wheezing, chest tightness, dry cough and sneezing. She worked in a shoe factory as a shoemaker, and was exposed to leather dusts for 14 yr, but she was not exposed to solvents, dyes or other known sensitizing agents. Her symptoms were worse when at work and when inhaling non-specific irritants.

At presentation, FEV_1 was 3.19 l (99% of predicted). The first nsBPT, performed when occasionally exposed to occupational agents, elicited a $PD_{15}FEV_1$ of 0.9 mg. Figure 1c shows the results of several nsBPT performed in the following period, during which there were long intervals of work cessation between short periods of work. Five weeks after cessation of work, $PD_{15}FEV_1$ fell

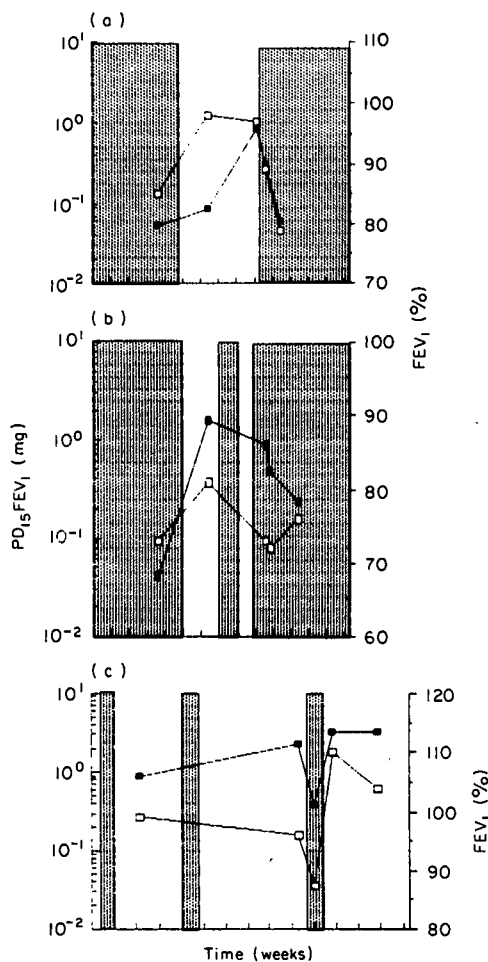


Fig. 1. Time course of FEV_1 ($\square$) and $PD_{15}FEV_1$ ($\blacksquare$) in three patients, during periods of work ($\blacksquare$) and work cessation, (a) patient 1, (b) patient 2, and (c) patient 3.

to a normal level (2.2 mg). Pulmonary function was evaluated during the first day of occupational exposure to work irritants after a long period of withdrawal; baseline FEV_1 was measured prior to starting the working shift and then hourly for 5 hr. After 1 h of exposure, a significant decrease in FEV_1 occurred (27% from baseline); nsBPT, performed 4 hr after the end of the work shift, when FEV_1 had returned to baseline values, showed a marked decrease in $PD_{15}FEV_1$ (0.38 mg). When the patient definitively ceased working, FEV_1 increased and NSBH disappeared ($PD_{15}FEV_1 > 3.2$ mg, 6 days, 1 month and 2 yr after cessation of work).

Discussion

Non-specific bronchial hyperresponsiveness can be induced by different occupational exposures; isocyanates and western red cedar dust are the most common [2,3],

but compounds such as colophony and other irritants [7,8] can also increase bronchial responsiveness to non-specific stimuli. In such cases, the agent thought to be responsible for the disease is well defined, and by means of a specific bronchial provocative test it is possible to reproduce asthmatic symptoms in the laboratory. In some occupational exposures, however, the identification of a single agent is often difficult. Bronchial challenge with some of the compounds supposed to be present in the work environment may give negative results, and the diagnosis of asthma may be unacceptable for legal purposes because of the lack of a certain aetiology. In these cases, the aetiological diagnosis may be performed by monitoring pulmonary function during work periods and holidays. In this study, FEV_1 is a sensitive parameter for the assessment of bronchoconstriction, but as bronchial obstruction in asthma is usually quickly reversible, laboratory measurement of FEV_1 may elicit no functional impairment even in the presence of disease; indeed, in two out of the three patients studied, baseline FEV_1 was always in the normal range (i.e. 80% of the predicted) except once.

Measurement of respiratory function by means of a peak flow meter during a work shift, or during a two-week period of work may be useful to show a work-related bronchoconstriction, but peak respiratory flow is not sensitive enough to detect small, even if significant, changes in respiratory function. Changes in NSBH can be used to assess an effect on the airways after exposure to sensitizing or irritant agents.

In the cases we report, a diagnosis of occupational asthma could be performed on the basis of an increase in NSBH during work exposure, and the recovery of NSBH after cessation of work. In effect, the changes in $PD_{15}FEV_1$ were greater than the usual variability of nsBPT in our laboratory ($\pm$ two doubling doses of methacoline). In these cases, it was not possible to perform specific bronchial provocative tests in the laboratory because of the difficulties in accurately reproducing a standardized exposure to such environmental irritants. The changes in NSBH, however, paralleled those in baseline FEV_1 , even if the latter were less relevant.

Furthermore, these observations confirm that NSBH can be shifted from a normal to an asthmatic range by several occupational exposures, represented in these cases by agents (solvents, dyes, exhaust gases, and leather dusts) not usually involved in inducing occupational asthma. Bronchial hyperresponsiveness to non-specific stimuli generally persists days to weeks after the causal event has occurred (viral infection of upper or lower respiratory tract, exposure to irritants or different 'sensitizing' agents) [1,3,9]. However, recovery of NSBH is not always observed, bronchial hyperreactivity may persist,

for a time dependent on the degree of exposure to the irritants [10] or on the duration or severity of the disease [11]. In our observations, $PD_{15}FEV_1$ methacholine considerably increased toward normal values 5–35 days after cessation of work, and the patient who definitively ceased work (No. 3) showed a long-lasting recovery of NSBH.

In conclusion, these three case reports confirm that NSBH can be induced by occupational exposure to different chemical irritants, and that the monitoring of bronchial hyperresponsiveness to methacholine can be a useful method to confirm occupational asthma.

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References

- 1 Lam S, Wong R, Yeung M. Non-specific bronchial reactivity in occupational asthma. *J Allergy Clin Immunol* 1979; 63:28–34.
- 2 Cockcroft DW, Cotton DJ, Mink JT. Non-specific bronchial hyperreactivity after exposure to Western Red Cedar: a case report. *Am Rev Respir Dis* 1979; 119:505–10.
- 3 Mapp CE, Polato R, Maestrelli P, Hendrick DJ, Fabbri LM. Time-course of the increase in airway responsiveness associated with late asthmatic reactions to toluene diisocyanate in sensitized subjects. *J Allergy Clin Immunol* 1985; 75: 568–72.
- 4 Cockcroft DW. Acquired persistent increase in non-specific bronchial reactivity associated with isocyanate exposure. *Ann Allergy* 1982; 48:93–5.
- 5 Brooks RM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 1985; 88:376–84.
- 6 Paggiaro PL, Bacci E, Talini D, Dente FL, Rossi O, Pulerà N, Fabbri LM, Giuntini C. Atropine does not inhibit late asthmatic responses induced by toluene-diisocyanate in sensitized subjects. *Am Rev Respir Dis* 1987; 136:1237–41.
- 7 Nadel JA, Salem H, Tamplin B, Tokiwa Y. Mechanisms of bronchoconstriction during inhalation of sulfur dioxide. *J Appl Physiol* 1965; 20:164–7.
- 8 Burge PS, Harries MG, O'Brien IM, Pepys J. Bronchial provocation studies in workers exposed to the fumes of electronic soldering fluxes. *Clin Allergy* 1980; 10:137–49.
- 9 Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976; 113:131–9.
- 10 Moller DR, Brooks SM, McKay RT, Cassedy K, Kopp S, Bernstein IL. Chronic asthma due to toluene diisocyanate. *Chest* 1986; 90:494–9.
- 11 Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to Western Red Cedar (*Thuja plicata*). *Am J Med* 1982; 72:411–15.

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