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Peak flow rate records in the diagnosis of occupational asthma due to isocyanates

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ABSTRACT Peak expiratory flow rate (PEFR) has been recorded hourly or two-hourly from waking to sleeping in workers with respiratory symptoms who were exposed to isocyanate fumes at work. Twenty-three recordings averaging 33 days duration were recorded in 20 workers. Each worker was also admitted for bronchial provocation testing to toluene di-isocyanate (TDI) or diphenylmethane di-isocyanate (MDI) fumes or both. A final assessment of work-related asthma made from subsequent work exposure was compared with the results of bronchial provocation testing and a subjective assessment of the peak flow records. Both techniques were specific and sensitive.

Physiological patterns of occupational asthma were defined from the records of PEFR. The most striking finding was the slow recovery from work-induced asthma. This commonly took several days to start and in one worker took 70 days to complete after leaving work. Several workers developed a pattern resembling fixed airways obstruction after repeated exposure at work. The consequences of these findings for the recording of symptoms of occupational asthma are discussed and recommendations are made for the recording of PEFR in workers in general.

Isocyanates were discovered by Wurtz in 1849 but commercial production was not started until the late 1930s. Their main use is in the production of polyurethanes, which are used in foams, adhesives, paints, lacquers, and electrical insulation. In 1951 Fuchs and Valade recorded that seven of nine workers exposed to toluene di-isocyanate (TDI) developed asthma. Since then there have been many reports of occupational asthma due to TDI fumes, though there are only a few good descriptions of the patterns of asthma at work (Sweet, 1968; Pepys *et al*, 1972; Siracusa *et al*, 1978).

A definitive diagnosis of isocyanate sensitivity can be made by bronchial provocation testing in hospital (Butcher *et al*, 1977; O'Brien *et al*, 1979). This is time-consuming and expensive and does not necessarily reproduce the working conditions, but is the best method currently available. Measurements of FEV_1 or peak expiratory flow rate (PEFR) before and after a workshift are widely used to try to record work-related asthma, but the results are often disappointing (Gandevia, 1963, 1964; Peters *et al*, 1968, 1969, 1970; Wegman *et al*, 1977).

Hourly records of PEFR at home and work have proved helpful in diagnosing occupational asthma caused by solder flux fumes containing colophony (Burge *et al*, 1979). We have tried to extend this to workers exposed to isocyanate fumes—that is, to provide objective evidence for occupational asthma, define the patterns of asthma, evaluate the usefulness of records of PEFR for diagnosis, and compare these with the history and bronchial provocation test in the same workers.

Methods

We studied the records of all workers investigated at Brompton Hospital who had kept a record of their PEFR for at least two weeks at home and work, and had been admitted for bronchial provocation testing to the fumes of TDI or MDI, or both. Twenty-three records of PEFR from 20 workers are included, the mean duration being 33 days (14–128). The workers were from three factories printing and laminating flexible packaging, where TDI or MDI was used occasionally in the printing ink and regularly for laminating. TDI levels measured in these factories were usually

0·001–0·007 ppm and excursions above the TLV (0·02 ppm) were extremely rare. Three workers were studied from a factory manufacturing printing ink where TDI was once used. During the recordings the source of isocyanate fumes was thought to be a neighbouring factory using polyurethanes, outside which levels of 0·004 ppm were recorded.

Each worker recorded his PEFR hourly, or in some cases two-hourly, from waking to sleeping as previously described (Burge *et al*, 1979). PEFR was measured using a Wright's peak flow meter (Wright and McKerrow, 1959) or gauge (Gregg, 1964).

Bronchial provocation tests were carried out in hospital with one exposure lasting 30 minutes on each day. FEV_1 was measured before challenge and regularly for at least 11 hours afterwards (O'Brien *et al*, 1979). A two part marine varnish was used to produce atmospheric concentrations of TDI of about 0·001 ppm. By adding small volumes of a mixture containing 10% free TDI atmospheric levels of about 0·002, 0·005, 0·007, 0·01, and 0·02 ppm could be achieved. The varnish without added TDI was used as a control. The test was considered negative if exposure to 0·02 ppm for 30 minutes did not result in a 15% fall in FEV_1 compared with the control day. Provocation testing to MDI fumes was achieved by heating MDI, 1 g, on a hotplate at 110°C for 20 minutes before exposure. This produced atmospheric levels of about 0·002 ppm. Levels of 0·007 and 0·02 were achieved by increasing the period of heating to 25 and 30 minutes respectively. Atmospheric isocyanate levels were always monitored using a UEI 700 continuous recording monitor, with additional personal samplers.

The peak flow records at home and work were plotted in the same form as the records of workers exposed to colophony fumes (Burge *et al*, 1979). Work-related asthma was diagnosed if 75% of the working weeks or weekends showed these specific patterns. In addition work-related asthma was diagnosed if there was a weekly pattern of deterioration at work and recovery away from work (vide infra). The record was called negative if specific daily patterns occurred in less than 25% of cases and there was no weekly pattern. Records were classed as inadequate if there was no repeating daily pattern and the record contained no prolonged period away from work.

Results

The physiological patterns seen have been divided into those occurring from hour to hour within one day (the hourly pattern), those occurring from day to day within one week (the daily pattern), and those occurring from week to week (the weekly pattern).

THE HOURLY PATTERN

The hourly pattern depended greatly on the shift being worked and the number of days previously spent at work, so these records varied considerably from day to day in the same worker. Figure 1 shows the hourly pattern of a gravure printer working on a 0600–1400 h shift and fig 2 a few days later on a 1400–2200 h shift. The late asth-

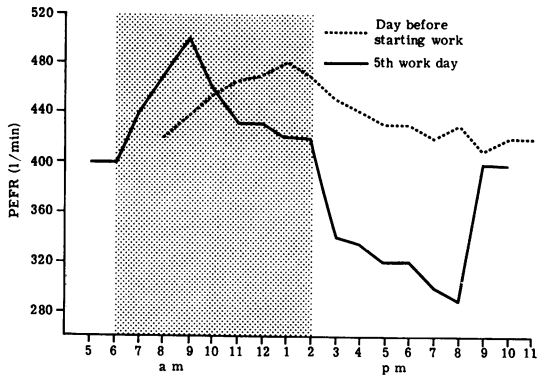

Fig 1 *Record of hourly PEFR in a gravure printer sensitive to isocyanate fumes liberated from a laminating machine in a neighbouring room. Working period is shaded. Day before starting work shows a normal diurnal variation. Fifth working day shows a pronounced late asthmatic reaction starting after leaving work.*

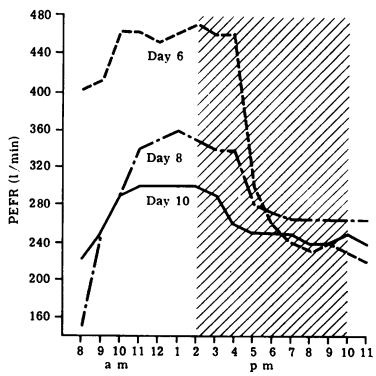

Fig 2 *Record of hourly PEFR in same gravure printer (fig 1). Dashed area shows work exposure on an afternoon shift. Late asthmatic reaction starts within two hours of coming to work. Day 10 shows a "flat" pattern with little evidence of an hourly work-related reaction.*

matic reaction occurred much sooner after exposure on the afternoon shift. By the tenth consecutive working day the diurnal variation had become much reduced with little evidence of recovery within the 24 hours (a "flat" record). Figure 3 shows the hourly record of a gravure printer who showed no 24-hour recovery after the first working day. This general depression of PEFR without a specific hourly pattern makes before and after shift measurements very misleading.

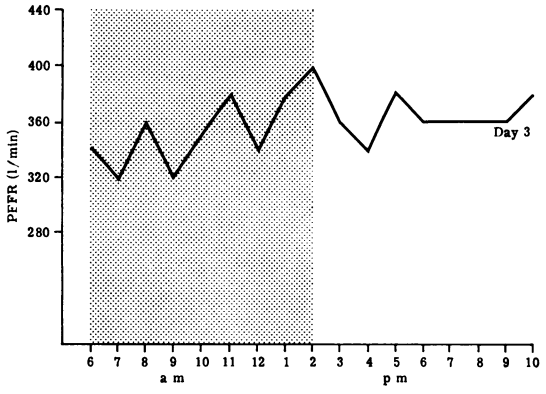

Fig 3 *Record of hourly PEFR of a slitter in a printing works where isocyanates are used for laminating. This shows a flat pattern on the third working day after a prolonged break (see fig 4).*

DAILY PATTERN

Only one worker exposed daily to isocyanate fumes had a regular daily pattern. He had one day off each week and had his highest mean PEFR on his first day at work, showing the "Monday best" recovery pattern seen in the electronics workers. He was worst at the end of the working week. Two other workers with intermittent exposures to isocyanate fumes had regular weekend recovery patterns when away from work for at least two days. There were no regular recovery patterns over weekends in the other workers.

The specific features of deterioration and recovery seen in workers exposed to isocyanates during the records are shown in table 1. The results are divided into those workers with a final assessment of work-related asthma, and those who were independently judged to have symptoms unrelated to work. Records from 27 "weeks" in affected workers showed specific daily deterioration patterns in 11 of 27 "weeks," most of which were the progressive daily deterioration pattern. No specific deterioration patterns were seen in the unaffected workers. Recovery patterns away from work were seen in eight of 24 weekends of affected workers and two of 18 weekends of unaffected workers.

WEEKLY PATTERNS

Weekly patterns were a prominent feature. The most common pattern seen was of progressive deterioration week by week until either a steady state was reached (fig 4) or the worker had to take time off to recover (fig 5). Altogether 67% of the records of affected workers showed a weekly deterioration pattern. Prolonged recovery patterns were often seen on removal from isocyanate fumes. Figure 6 shows the record of an ink maker who left work three weeks before the recording started and was exposed for one day during a recovery that took 70 days. Figure 7 shows his progressive deterioration on return to work. There were six recordings from sensitised workers that included at least nine days of readings after a period of exposure. One of these started to improve on the first day away from work, but the start of improvement was delayed 4–12 days in the remainder (figs 4 and 5). The recovery period was often associated with increasing diurnal variation in PEFR (fig 8).

Table 2 shows the results of subjective assessments tests of PEFR records (made without knowledge of work exposure to isocyanates or of

Table 1 *Specific deterioration and recovery patterns seen in the PEFR records. Percentages of total recorded weeks at work and weekends away from work*

Final assessment	*Deterioration*				*Total recorded weeks at work*	*Recovery*		*Total weekend recorded*
	Each working day equivalent	*First day worse*	*Last day worse*	*Progressive weekly deterioration*		*Sat/Sun*	*Mon*	
Work-related asthma, exposed to isocyanate during record	4%	11%	26%	67%	27	25%	8	24
No work-related asthma, exposed to isocyanate during record	0	0	0	0	20	11%	0	18

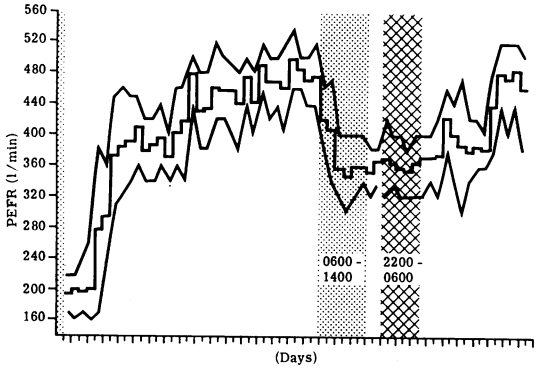

Fig 4 *Record of daily maximum (upper line), mean (middle line), and minimum (lower line) PEFR in same slitter (fig 3). Days worked on a morning shift are shaded, and crosshatched on a night shift. Days at home have a plain background. Record started after a prolonged period at work. Improvement started four days later and was largely complete 26 days later. Return to work was followed by progressive deterioration soon resulting in a flat record with no improvement on days off. Recovery was again prolonged in period off work at end of recording.*

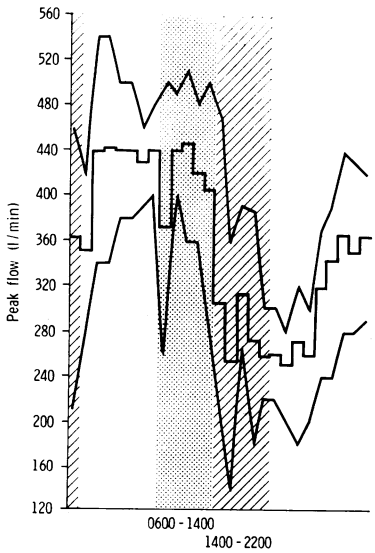

Fig 5 *Record of daily maximum, mean, and minimum PEFR in gravure printer (figs 1 and 2). He visited medical centre for two hours on first day of record after a prolonged period away from work; this resulted in two days' asthma. There was a pronounced fall in PEFR on first working day followed by recovery and then progressive deterioration until a relatively flat record occurred. Start of recovery was delayed for five days, and was still incomplete nine days after leaving work.*

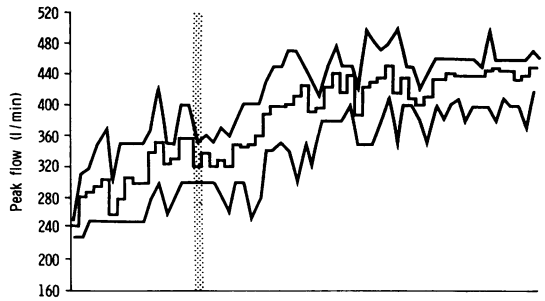

Fig 6 *Record of daily maximum, mean, and minimum PEFR in an inkmaker exposed to isocyanate fumes from a neighbouring factory. He left work three weeks before recording started. His recovery took 70 days and was delayed for about five days by a 30-minute exposure to isocyanate fumes during recording. His further records are shown in fig 7.*

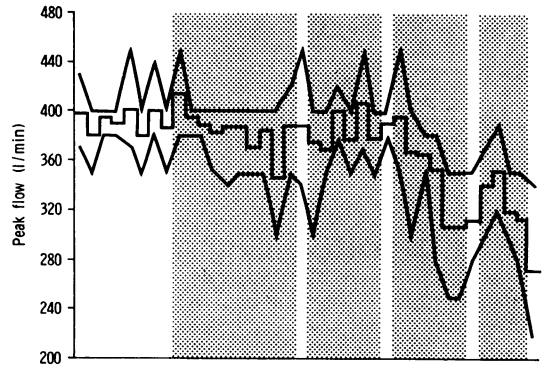

Fig 7 *Record of daily maximum, mean, and minimum PEFR in an inkmaker exposed to isocyanate fumes from a neighbouring factory (see fig 6). Deterioration started in the third working week and progressed further in the fourth working week. He was admitted to hospital with severe asthma three weeks later. This prolonged cycle has now been repeated three times.*

the results of the final diagnostic assessment and of the provocation tests). Five workers had been removed from exposure before the recordings were made, and three sensitised workers kept additional records when no longer exposed to isocyanate fumes. These results are presented separately. Work-related asthma was diagnosed from the PEFR records in six cases from the week-by-week patterns of deterioration at work followed by recovery away from work. Five of the recordings were inadequate because they contained no regular daily pattern and no prolonged period away from work.

Bronchial provocation testing was positive in 12 workers, all with a final assessment of work-

Table 2 *Subjective assessment of PEFR records and results of bronchial provocation testing*

Final assessment	*No*	*Challenge positive*	*Subjective assessment*				*Maximum diurnal variation in PEFR*			
			Work-related asthma	*Equivocal*	*Not work-related*	*Inadequate*	*> 50%*	*30–49%*	*< 30%*	*< 15%*
Work-related asthma exposed to isocyanate fumes during record	9	7	8			1	5	3	1	
Work-related asthma, not exposed to isocyanate fumes during record	6	6		1	4	1	1		2	3
No work-related symptoms, exposed to isocyanate fumes during record	6	0			4	2		1	2	3
No work-related symptoms, not exposed to isocyanate fumes during record	2	0			1	1			2	

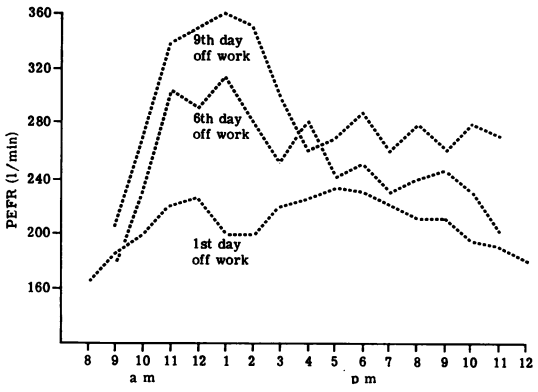

Fig 8 *Record of hourly PEFR in gravure printer shown in figs 1, 2, and 5. Record shows progressive recovery after leaving work with increasing diurnal variation. Morning dip still persisted on ninth day after leaving work.*

related asthma. Eleven of these had dual immediate and late asthmatic reactions with the late component being predominant; one had a late asthmatic reaction alone. One worker reacted at an isocyanate concentration of 0·001 ppm and all the others reacted at 0·005 ppm or less.

Table 3 shows the sensitivity and specificity of the peak flow record assessments and bronchial provocation tests compared with the final assessment made from the subsequent course of the asthma on re-exposure at work. All exposed workers with adequate records had a subjective assessment of work-related asthma; the assessments were negative in non-sensitised workers.

Bronchial provocation testing failed in two sensitised workers. In one the testing had to be abandoned because of a low baseline FEV_1 and the other was negative.

Table 3 *Sensitivity and specificity of bronchial provocation tests with MDI or TDI or both, and subjective assessment of adequate PEFR records in exposed workers*

	Sensitivity %	*Specificity %*	*Potential number of positive assessment*	*Potential number of negative assessment*
Bronchial provocation testing	83	100	12	8
Subjective assessment of peak expiratory flow rate records	100	100	8	4

Discussion

The workers we studied were a selected group as all had been referred to Brompton Hospital. Those with the most severe symptoms were unlikely to have been included as they have usually removed themselves from exposure before being seen. Plotting of the daily mean, maximum, and minimum PEFR has proved an easy way of interpreting the large number of readings.

The workers studied came from factories where the concentrations of TDI or MDI were low and levels over the TLV had not been recorded in workers' breathing zones in any of the factories.

The patterns of reaction differed considerably from those following exposure to colophony fumes. The day-to-day patterns of peak flow showed few regular patterns, as were seen in the colophony-exposed workers, while after exposure had ceased several days usually elapsed before recovery began.

The hour-by-hour patterns of peak flow depended on the shift being worked and on the time since the last prolonged break from work.

Reactions started sooner after starting work on an afternoon shift than on a morning shift. This is likely to result from two additive effects. The normal diurnal variation would produce increasing values from waking for about six hours before falling again. A reaction due to work would thereafter be less evident in the morning than in the afternoon. The situation on the night shift depends on the sleeping pattern of the worker. Records in unsensitised workers did not differ significantly between the three shifts. This finding is similar to that of Guberan *et al* (1969) who found an increase in PEFR of 4·1% on a 0600–1400 h shift, a mean decrease of 1·5% on a 1400–2200 h shift, and no change on a 2200–0600 h shift. Walford *et al* (1966) found trivial changes on the three shifts in asymptomatic cotton workers, but in symptomatic workers the drop in $FEV_{0·75}$ was greatest on the night shift (0·16 l, 0·25 l, and 0·33 l respectively). The men studied on each shift, however, were different and the relationship to sleep was not stated.

The patterns of reaction seen in this study have considerable implications for those studying long-term changes in lung function in workers exposed to isocyanates. Clearly recovery is unlikely to occur during a two to three day break between ordinary work periods, which means that the value obtained on arrival on the first day of the week is unlikely to be a baseline reading in sensitised workers but represents the effects of previous exposure. Maximal recovery in one of our workers took 70 days. Measurement of lung function before and after a working shift may well miss the late reaction occurring at home, but more importantly several workers entered a state of "fixed" airways obstruction with little diurnal variation after one to four weeks at work. Readings taken before and after shifts in this state are unhelpful.

We have now performed bronchial provocation testing on 80 workers exposed to isocyanate fumes. Provocation testing to concentrations up to the TLV of 0·02 ppm for 30 minutes has been shown to be highly specific, there having been no false-positive reactions. Provocation testing failed in two workers, in one of whom the test had to be abandoned because of a low baseline FEV_1. Possibly the one worker with clear occupational asthma and a negative provocation test may have been sensitive to another agent. It is in this situation that the recording of peak expiratory flow rate at home and work is particularly useful as it provides a means of checking the provocation test results.

The records of peak expiratory flow rate have been more difficult to assess than in the electronics workers because of the irregular work shift, short periods off work, and prolonged periods of recovery. Nevertheless, by increasing the length of the record and including a prolonged period off work, highly sensitive and specific results have been obtained, which form a suitable alternative to provocation testing in the worker who is still exposed at work. Treatment with sodium cromoglycate or corticosteroid has not masked the changes seen in three workers who were taking them.

The workers described here form a group at the severe end of the spectrum of occupational asthma, whereas the colophony exposed workers are nearer the centre. Conclusions from these two studies may well be applicable to occupational asthma in general. We have shown that it is possible to obtain hourly records of peak expiratory flow rate from a wide range of workers. Many of the most complete and apparently reliable records came from the least intelligent workers, who were often working on production lines with short repetition times. Most of the records with prolonged periods off work were taken over the Christmas and summer holidays when good records were achieved. Keeping these records has been a considerable imposition on these workers, but has not resulted in the loss of earnings that often results from hospital admission for bronchial provocation testing.

The records obtained in sensitised workers consistently showed the hourly, daily, and weekly patterns described. These patterns were infrequently seen in workers without occupational asthma. Subjective analysis of these results proved to be sensitive and specific for the recording of occupational asthma and verified the results of bronchial provocation testing. The failures of the peak expiratory flow rate records resulted largely from recordings that were too short. Before a record is considered negative it should include a period at work without corticosteroid or cromoglycate treatment followed by at least 10 days off work, followed by at least two weeks at work. The records should be made at least two-hourly, and the worker should be exposed to the suspected offending agent during the recordings. It is often possible, however, to make a definite diagnosis on records much shorter than this. These records may mean repeated exposure at work without close medical supervision. It is safer to admit those with severe symptoms to hospital for controlled bronchial provocation testing if objective evidence of work-related asthma is required.

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