under his clinical care. This was a man who had received heavy exposure and remained persistently disabled by dyspnœa; though he could scarcely walk across the room and his vitalograph tracings showed a very bad respiratory function, Dr Colin Ogilvy, who carried out full respiratory function tests upon him, reported all as normal. Dr Caldwell felt that although there was a large element of compensation neurosis in this case, there was also genuine persistent disablement.

The second patient was a fit young man who, following exposure to TDI, had become so sensitized that he only had to go into a shop where the substance was being sprayed and he had an attack of asthma. When he was away from the atmosphere he was perfectly fit.

The third case was another one of very heavy exposure who appeared to remain persistently breathless with some diminution of FEV_1 and vital capacity, and whose breathlessness appeared to be aggravated by alcohol.

Dr Caldwell expressed disappointment that the speakers had not given more descriptions of clinical cases of TDI exposure.

Dr W M Dixon (*London*) said he had seen 2 cases of allergic bronchial asthma in a factory in which TDI had never been used. Both workers had been exposed to a fine droplet spray of MDI during maintenance and testing of a dismantled mixing head. As MDI did not vaporize at room temperature he asked how this toxic effect had occurred; he had always assumed MDI to be safe because of its higher temperature of vaporization. He also suggested that a register of cases of isocyanate sensitivity should be established by a joint research committee of the British Tuberculosis Association and the Society of Occupational Medicine.

Dr A O Robson (*High Wycombe*) said that he saw a number of cases of 'French polishers' who in fact did not French polish but sprayed furniture with MDI or cellulose sprays. A number of them got respiratory symptoms and he wondered whether this was due to MDI or if it could be one of the catalysts.

Dr A Munn replied that the inhalation of droplets of MDI could certainly bring about an attack of an asthmatic type of bronchitis. Such symptoms could be attributed to the primary irritant effect of MDI, and did not represent sensitization. Sensitization might follow, in which case respiratory symptoms might be experienced after exposure to MDI at ambient temperatures. Whilst it was true to say that MDI was of low volatility at ambient temperature, it was misleading to suggest that it did not volatilize at all. Atmospheric concentrations of vapour above, or even approaching, the Threshold Limit Value would not occur at room temperature, but sensitized individuals might develop respiratory symptoms from exposure to concentrations well below the TLV, levels which might be so low that they could not be measured at all. With MDI, such cases were rare.

Studies of Isocyanate Toxicity

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Cumulative Pulmonary Effects in Workers Exposed to Tolylene Diisocyanate

The range of clinical effects of tolylene diisocyanate (TDI) on the respiratory system has been summarized by Brugsch & Elkins (1963). The asthma-like syndrome is perhaps the most widely known effect of TDI.

Gandevia (1963) and Williamson (1965) reported on acute changes in ventilatory capacity occasioned by exposure to relatively high concentrations of TDI. Because of this we were curious to see if low concentrations of TDI would produce changes in ventilatory capacity.

Our first survey involved 38 workers involved in pouring polyurethane foam. The factory was modern and by appropriate ventilation air concentrations had not been found to exceed 0·02 ppm, the threshold limit value.

Ventilatory capacity was assessed by recording forced vital capacities on a 13·5 litre spirometer with a fast kymograph speed of 1920 mm/min. Five readings were recorded before and after the day shift. From these tracings we derived the FVC, FEV_1, and flow rates at various lung volumes. For simplicity the FEV_1, the mean of the last 3 of 5 trials, was used as the principal index of ventilatory capacity. In addition a standard respiratory questionnaire was administered. The measurements of ventilatory capacity were made on Monday after a weekend of no exposure.

Of 38 workers studied to determine acute changes during a day, 34 showed a decline in FEV_1 with a mean fall of 0·22 litres. The highest concentration of TDI noted during this day was 0·003 ppm. On Friday afternoon the measurements were repeated and the FEV_1 was still depressed. Complete details of this part of the study appear elsewhere (*see* Peters *et al.* 1968).

We were somewhat surprised at the magnitude and the consistency of these changes in FEV_1 with the very low levels of TDI. This led us to conduct a similar survey six months later. In addition to measurement of FEV_1 made Monday morning and afternoon, we also determined the FEV_1 on Tuesday morning and afternoon. This

was to assess whether overnight recovery was complete, partial, or non-existent.

The results of this survey are summarized in Table 1 and published in detail elsewhere (Peters *et al.* 1969). Two important points can be made from these data: the first is that the acute change is again present with a mean fall in the FEV_1 of 0·16 litres, the second is that complete overnight recovery does not occur. The mean FEV_1 on Tuesday morning was significantly lower than the Monday morning value at the $P<0·01$ level. The highest level of TDI measured during this second survey was 0·012 ppm. Thirty-four workers were examined during this second survey.

Table 1
Means of FEV_1 in 34 workers exposed to TDI (litres)

	a.m.	*p.m.*
Monday	3·92	3·76
Tuesday	3·82	3·79

There were 28 workers common to both of the first two surveys; so, to assess the cumulative effect, if any, of exposure to low levels of TDI, we compared the FEV_1 taken on Monday morning of the first survey with that taken on Monday morning six months later. These data are presented in Table 2. A statistically significant mean decrease in the FEV_1 of 0·14 litres had occurred over the six months.

Table 2
Mean of FEV_1 in 28 workers exposed to TDI for six months

	First survey	*Six months later*	*Difference*	*P*●
FEV_1 (litres)	4·07	3·93	0·14	<0·02
Maximum TDI (ppm)■	0·0003	0·012		

● Paired *t* tests
■ Highest level of TDI measured

By now we began to wonder if any level of TDI, however small, might produce these changes in ventilatory capacity. To pursue this we returned to the factory six months later for the third time and repeated our measurements of FEV_1 on Monday morning and afternoon. Much to our surprise, the mean decrease during the day was very small, 0·05 litres (*see* Table 3). A few days later, when we received the aerometric data for TDI, the findings were explained. The peak concentration detected was only 0·0015 ppm.

Table 3
Mean of FEV_1 in 43 workers exposed to TDI (litres)

a.m.	*p.m.*	*Difference*	*P*●
3·81	3·76	0·05	<0·05

● Paired *t* tests comparing difference of means (TDI)=0·0015

Twenty-five workers were common to the first and third surveys one year apart. Table 4 presents the mean of FEV_1 for each of these two time periods. There was a statistically significant decline in FEV_1 over one year, but the first six months accounted for all of it. That is, between second and third surveys no change had taken place.

Table 4
Mean of FEV_1 in 25 workers exposed to TDI for one year

	First survey	*One year later*	*Difference*	*P*●
FEV_1 (litres)	4·07	3·95	0·12	<0·02
Maximum TDI (ppm)■	0·003	0·0015		

● Paired *t* tests
■ Highest level of TDI measured

We have now measured workers in this factory on 5 occasions separated by six months over a two-year period. On four of five surveys we have observed acute changes in the FEV_1 which have averaged from 0·16 to 0·22 litres during the full production pouring. The lone exception has been cited above on a day when TDI concentrations were very low.

Table 5 summarizes the change in FEV_1 occurring over two years, the mean decline for 20 workers being 0·22 litres. Since the decrement during the first year was 0·12 litres, for the two years that these workers have been followed the mean annual decline has been 0·11 litres.

Table 5
Mean of FEV_1 in 20 workers exposed to TDI for two years

	First survey	*Two years later*	*Difference*	*P*
FEV_1 (litres)	4·11	3·89	0·22	<0·01
Peak TDI (ppm)	0·003	0·0125		

There seems to be little question about the reality of the acute changes in FEV_1. Excellent studies by McKerrow *et al.* (1958), Lewinsohn *et al.* (1960), Bouhuys *et al.* (1963), Walford *et al.* (1966) and Guberan *et al.* (1969) have essentially ruled out diurnal variation as an explanation for our findings.

The meaning of the longitudinal decrement in FEV_1 that we have observed is less certain. Data are available on expected decrement over time in normal general populations, normal working populations, and in groups of patients with chronic, non-specific lung disease. These data are summarized in Table 6. It can be seen that in normal populations the rate of fall is from about 0·025 to 0·047 litres per year. In patients the rate of decline is greater, being about 0·08 litres per year.

Table 6
Longitudinal decrements in FEV

Authors	*Year of report*	*Type*	*No. of subjects*	*Sample*	*Fall in FEV/year (l)*
Kory *et al.*	1961	Cross-sectional	468	Selected normals	0·028
Higgins & Oldham	1962	Longitudinal	253	Men, random●	0·047
Ferris *et al.*	1965	Cross-sectional	1,221	General population, random	0·025
Medical Research Council	1966	Longitudinal	373	Patients	0·079
Jones *et al.*	1967	Longitudinal	100	Patients	0·046
Howard	1967	Longitudinal	125	Patients	0·083
Higgins *et al.*	1968	Longitudinal	594	Men, random	0·031
					0·052
Burrows & Earle	1969	Longitudinal	200	Patients	0·084
Peters *et al.*	1969	Longitudinal	20	TDI workers	0·110

●Many miners and foundrymen

It may be presumptuous to include our data in such a tabulation because admittedly we have studied a small group over a relatively short time period. However, if this observation is verified by others or by ourselves on other similarly exposed workers, it is very important.

We observed that the workers showing the large acute changes in FEV_1 are the ones likely to show sizable cumulative effects. Correlation coefficients have been calculated for these two variables and appear in Table 7. The correlation is sizable and consistent. This information might be useful for screening and placement of workers in this industry.

Table 7
Correlation of one-day changes in FEV_1 with six-month and one-year changes

	Six months	*One year*
r	0·72	0·71

Workers with chronic cough and sputum respond much more dramatically to TDI exposure. Table 8 compares changes over one day of symptomatic and asymptomatic workers. The changes are twice as great in the symptomatic. Considering the changes over six months, symptomatic workers have ten-fold greater declines (*see* Table 9). This information should also have some practical application in screening and placement.

Table 8
Comparison of symptomatic with asymptomatic workers: mean decrease in FEV_1 over one day

	Symptomatic		*Asymptomatic*		
	Decrease in FEV_1 (litres)	*No. of cases*	*Decrease in FEV_1 (litres)*	*No. of cases*	*P*
Cough	0·42	6	0·18	32	<0·01
Sputum	0·35	10	0·17	28	<0·02

Table 9
Comparison of symptomatic with asymptomatic workers: mean decrease in FEV_1 over six months

	Symptomatic		*Asymptomatic*		
	Decrease in FEV_1 (litres)	*No. of cases*	*Decrease in FEV_1 (litres)*	*No. of cases*	*P*
Cough	0·55	5	0·05	23	<0·01
Sputum	0·4	8	0·04	20	<0·01

The effect of smoking does not seem important. There was no statistically significant difference between smokers and nonsmokers for acute effects seen during one working day (21 nonsmokers showed a mean fall in FEV_1 of 0·2 litres and 17 smokers 0·23 litres). For the cumulative effects of TDI, 9 smokers showed an average fall of 0·22 litres and 11 nonsmokers a fall of 0·23 litres.

Conclusion

(1) Acute changes in ventilatory capacity occurred in workers exposed to TDI at levels below the threshold limit value.
(2) These acute changes in FEV_1 did not recover overnight.
(3) Cumulative changes were observed in workers during the first two years of this survey, which exceeded those expected from ageing. Whether these changes will reverse with a cessation or lowering of exposure is not known.
(4) Workers with chest symptoms demonstrated a greater acute and cumulative response to TDI than asymptomatic ones.
(5) A highly significant correlation between one-day change and cumulative change was observed.

Further studies are planned or are under way to confirm or refute these observations in other similarly exposed groups.

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A Controlled Study of Workers Handling Organic Diisocyanates

A study of workers handling naphthylene diisocyanate (NDI) and prepolymerized tolylene diisocyanate (TDI prepolymer) in the manufacture of foamed and unfoamed urethane elastomers was carried out over a year, using controls drawn from similar work in the same factory but not handling isocyanates. The study was undertaken because of complaints by the exposed workmen that they were suffering from bronchitis. It was already known that a few cases of asthma had occurred in the course of this work, but prior to the study occasional atmospheric measurements of NDI had all been below a threshold limit value of 0·17 mg/m^3 tentatively proposed for this substance (0·17 mg NDI ≡ 0·14 mg TDI).

The study consisted of full medical examinations at the start and end of the period, together with one-second forced expired volume (FEV_1) and forced vital capacity (FVC) measurements. At the end the revised MRC Standard Questionnaire on Respiratory Diseases was completed. All episodes of respiratory illness during the year were recorded, whether causing absence or not.

Three groups emerged: (1) An exposed group having regular contact with NDI vapour and to a lesser extent TDI. (2) A neighbourhood group composed of people with intermittent and lesser exposure. (3) The non-exposed control group. The exposed and neighbourhood groups had all had pre-employment medical examinations before originally starting such work and the same criteria were applied in establishing the control group.

Chest illness was defined as: (1) Chronic bronchitis for the past three years as defined by the College of General Practitioners in 1961. (2) Episodes of chest illness of bronchitic type occurring within the three years up to the end of the study. (3) Episodes of chest illness with or without absence during the review period of one year.

Statistical analysis of the results showed a significant association between exposure to isocyanates and chest illness with or without absence from work during the review period amongst the exposed group ($P<0·05$). There was also a significant relationship between regular or occasional exposure in the exposed and neighbourhood groups combined and episodes of chest illness of bronchitic type for the past three years ($P=0·017$).

The control group showed an average deterioration in FEV_1 over the year of 0·11 litres and of 1·6% in FEV_1/FVC ratio, which was significant, $P<0·05$. The FEV_1 and FVC in the exposed group and the FEV_1 in the neighbourhood group showed deteriorations which were not statistically significant. The neighbourhood group, whose mean age was significantly greater than that of the exposed or control groups, showed a fall in FVC of 0·09 litre ($P<0·02$). Comparisons *between* the groups, however, showed no significant differences in FEV_1, FVC or FEV_1/FVC.

No significant differences were found in smoking habits and FEV_1/FVC or chest illness, lung function and chest illness, lung function and past dusty work or chest illness and past dusty work.

The study demonstrated that there is an association between exposure to isocyanates (particularly NDI) and episodes of chest illness of all types during the period and of episodes of chest illness of bronchitic type during the three years prior to the end of the period. This confirmed that the complaints of 'bronchitis' made by the exposed workmen were justified.