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Persistent respiratory effects in survivors of the Bhopal disaster

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Introductory article

Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: a cross sectional survey

P Cullinan, S Acquilla, N Ramana Dhara, on behalf of the International Medical Commission on Bhopal

Objective. *To examine the role of exposure to the 1984 Bhopal gas leak in the development of persistent obstructive airways disease.* ***Design.*** *Cross sectional survey.* ***Setting.*** *Bhopal, India.* ***Subjects.*** *Random sample of 454 adults stratified by distance of residence from the Union Carbide plant.* ***Main outcome measures.*** *Self reported respiratory symptoms; indices of lung function measured by simple spirometry and adjusted for age, sex, and height according to Indian derived regression equations.* ***Results.*** *Respiratory symptoms were significantly more common and lung function (percentage predicted forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$), and FEV_1/FEV ratio) was reduced among those reporting exposure to the gas leak. The frequency of symptoms fell as exposure decreased (as estimated by distance lived from the plant), and lung function measurements displayed similar trends. These findings were not wholly accounted for by confounding by smoking or literacy, a measure of socioeconomic status. Lung function measurements were consistently lower in those reporting symptoms.* ***Conclusion.*** *Our results suggest that persistent small airways obstruction among survivors of the 1984 disaster may be attributed to gas exposure.* *(BMJ* 1997;**314**:338–43)

The effects of inhalation of a highly irritant gas on the subsequent morbidity of long term survivors is the question addressed in this population based survey of symptoms and lung function carried out among the general population living in Bhopal, Madhya Pradesh.[1] Over a period of nine days a randomly selected sample of 454 adults who in 1994 were living along the path believed to have been followed by a cloud of methyl isocyanate vapour on 3 December 1984 were interviewed. All gave information about their own exposure and their current respiratory symptoms. A randomly selected 20% of these were invited to have spirometric tests before and after salbutamol and results were obtained on 74, 82% of those selected.

Respiratory symptoms inquired about were breathlessness when walking on the level or climbing hills; cough for more than three months; phlegm for more than three months; and wheeze in the past year. Symptoms and lung function were analysed in relation to distance from the source of the gas release, based on the assumption that the inhaled concentration of vapour diminished by dilution with ambient air as the cloud moved southward from the pesticide manufacturing plant.

Other factors which could contribute to respiratory symptoms (smoking, age, sex, and socioeconomic status) were accounted for in the analysis by separating out groups stratified by these factors to determine whether confounding—for example, higher prevalence of smoking among those living closer to the plant—could explain the observed association between proximity to the plant on the night of the methyl isocyanate release and the presence of symptoms and pulmonary defects 10 years later.

Figure 1 shows symptoms in relation to the distance subjects lived from the plant in 1984. Symptoms specific for airway pathophysiology (phlegm, strongly correlated in previous anatomicopathological studies with mucus gland hypertrophy)[2] and wheeze (the symptom most strongly correlated with airway hyperreactivity in previous studies),[3] had the lowest prevalence in both the exposed and control (residence >10 km from the plant) populations. It is not clear from this paper whether subjects were asked about "phlegm on most days for more than three months each year, for two or more consecutive years", the question often used to define chronic bronchitis in epidemiology. Yet although dyspnoea was reported in 50% of those living at a great

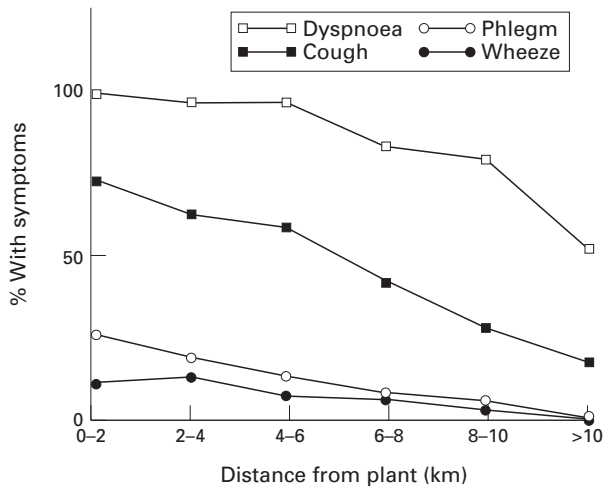

Figure 1 Trends in reported respiratory symptoms in 454 survivors 10 years after the Bhopal incident, still living in their original residences, according to distance from the Union Carbide plant. Reproduced with permission from Cullinan et al.[1]

distance from the plant, a consistent gradient in symptoms was seen for each of the symptoms.

Part of the gradient seen in fig 1 could be associated with a trend for lower income (lower socioeconomic status is usually strongly associated with respiratory symptoms) in those who had lived closer to the plant. However, the opposite trend (higher symptoms with greater distance from the plant) would be expected based on the higher reported "ever" smoking rate among those living at a greater distance from the plant. It should be noted that the overall prevalence of ever having smoked cigarettes in the interviewed population was 14%, consistent with the low current overall smoking prevalence in India compared with the UK or USA.

Less susceptible to potential reporting bias are the lung function measurements (fig 2) expressed as percentage predicted for a reference non-smoking adult Indian population reported in 1987. While a relationship between proximity to the plant and lower percentage predicted lung function might be suspected from examining the figure, a statistically significant result was seen only for mid expiratory flow rate ($FEF_{25–75}$). Particularly when the mean effect observed is relatively small, one cannot be sure whether the same association would be seen if the 19% of individuals randomly selected but never tested had also been included in the study.

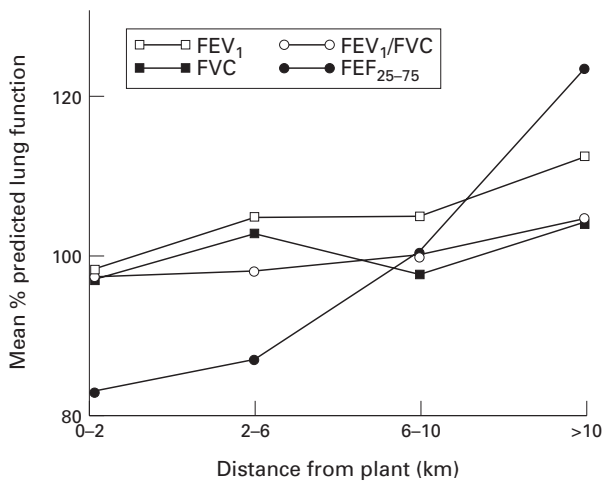

Figure 2 Relation between respiratory function and distance lived from the Union Carbide plant in 74 survivors 10 years after the Bhopal incident. Percentage predicted lung function is based on published norms in Northern Indian adults. Reproduced with permission from Cullinan et al.[1]

Stratification of these subjects by smoking history weakened but did not abolish the association between estimated exposure and lower mid expiratory flow rate. The number of subjects in the lung function study (74) did not permit multivariable analysis which allows independent examination of the size of the effect of different factors (such as proximity to the plant and smoking). Only two of the 74 subjects tested, both of whom had lived <2 km from the plant, had an increase in forced expiratory volume in one second (FEV_1) of 200 ml and >15% after salbutamol.

The investigators do not address the possible effect on respiratory symptoms of current air pollutant exposures in relation to distance from the Union Carbide plant. Very large cities may have gradients of ambient pollution exposure, symptoms, and lung function related to variability in exposure between neighbourhoods.[4] Whether such an effect might be present in Bhopal at the present time is not discussed.

Thus, in summary, the investigators observed a correlation between a crude estimate of past exposure to irritant gas and current symptoms and mid-expiratory flow rate, but not with FEV_1, in survivors of the Bhopal episode.

Significance of the study

After a disaster in which thousands died mainly from respiratory failure in the first hours and days after exposure, what is the point of demonstrating a residual effect on the lungs of survivors? In addition to the provision of medical care and compensation to victims, what are the scientific implications?

The surprising answer is that relatively little is known about the long term outcome for adults who survive a single major "gassing" episode such as this. The broad implications of Bhopal for the safety of communities living near major industries were immediately evident. Such communities become more frequent as many of the world's large industrial cities continue to expand. The number of citizens affected was unprecedented but similar exposures, usually to much less irritant clouds, are a frequent occurrence in industry and have been an occasional occurrence in community episodes worldwide. Clinical experience with small numbers of patients affected in such episodes would suggest that most survivors who become symptomatic within hours after exposure are nonetheless free of residual effects 10 years later. Yet follow up of a number of severely affected groups has also shown that long term effects are possible.

As is the case with all epidemiological studies, this study can only demonstrate associations—in this case the association between distance from the origin of the toxic cloud and the prevalence of symptoms and lower $FEF_{25–75}$. Yet it adds an important dimension to follow up of Bhopal survivors by its random selection of subjects and use of an objective, if only approximate, surrogate index of exposure. The importance of the random selection of subjects made in this study cannot be overemphasised. After a major toxic exposure, avoiding bias in the selection of study subjects can only be overcome by this approach. The group studied is representative of survivors still living in the community and omits those who died from any cause during the 10 years after exposure and those who left the community. Demonstration of cause and effect associations are

beyond the scope of any epidemiological studies. Most studies of respiratory response to environmental exposures are weakened by imprecise estimates of exposure of the respiratory system. This quantitative uncertainty in exposure results in quantitative uncertainty about the magnitude of the effect.

The lack of a larger and more comprehensive epidemiological follow up of Bhopal survivors has been noted,[5] yet follow up studies conducted by a number of groups have produced a coherent, though incomplete, picture of the natural history of methyl isocyanate inhalation toxicity. This latest study, conducted on behalf of the International Medical Commission on Bhopal, adds important new perspectives to that picture.

Within hours of the event, groups of affected patients were assessed and then followed up by several different investigators. The degree to which information from such small cohorts is applicable to larger groups depends on how representative the cohorts are of the larger groups. From the many follow up cohorts I have selected two. Patients who presented with respiratory symptoms were followed up with bronchoalveolar lavage (BAL) and pulmonary function testing,[6] and with sequential respiratory and immunological testing at 3, 6, 12, 18, and 24 months.[7] The selection of subjects in these studies was on initial clinical illness, so these groups can be considered to have been less exposed than those who died within the first weeks after the event, but more exposed than the random population sample chosen by Cullinan *et al*.[1] Even so, within these groups there may be overlap in disease severity, particularly as Cullinan *et al* chose a random sample living far away from the gas release, assumed to be healthy controls.

Kamat's follow up cohort consisted of patients reporting exposure and immediate illness who had detailed clinical, physiological and psychological follow up for which they travelled 675 km to Mumbai or were Mumbai residents visiting Bhopal in 1984. The investigators noted an initial improvement in symptoms over the first 12 months with a subsequent worsening over the next 12 months. Two years after exposure, dyspnoea and cough were more prevalent than phlegm, as in Cullinan's population based study. Lung function improved over the first year and at two years declined slightly, with a restrictive pattern. It is interesting to note that the mid-expiratory flow rate alone appeared to decline progressively over the period of observation. As is often the case in cohort studies, dropout of subjects can introduce bias with effects difficult to estimate.

Vijayan and Sankaran[6] excluded patients with a history of respiratory disease and included patients from a clinic for disaster victims and symptomatic exposed subjects from the community. Their 60 subjects were studied once from one to seven years after exposure. The severity of exposure was based on initial illness severity (including death of a household member). Using predicted values from North Indian subjects (but different from those used by Cullinan *et al*) and a group of control subjects, they noted an association between initial disease severity (as a surrogate for exposure) and impaired lung function. Obstructive as well as restrictive patterns were seen in the more severely affected. More severe abnormalities on spirometric tests were seen in those estimated to have had higher exposures, including those without a history of smoking (fig 3). Total cell counts (predominantly macrophages) were significantly higher in the BAL fluid of non-smokers with severe exposure. Interstitial markings on the radiograph were noted in both this group and Kamat's, possibly also a result of acute lung injury.

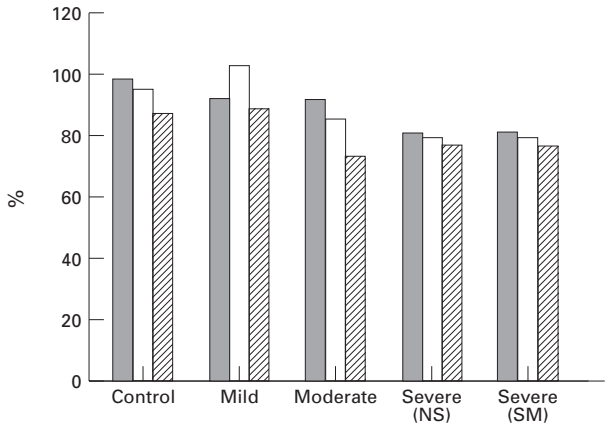

Figure 3 Pulmonary function results in relation to severity of exposure in 60 patients with persisting respiratory symptoms 1–7 years after the Bhopal incident. One way ANOVA: FEV_1/FVC% declined as severity of exposure increased ($p=0.05$). NS=non-smoker; SM=smoker; ANOVA: analysis of variance. Dark stippled bars=FVC % predicted; open bars=FEV_1 % predicted; striped bars=FEV_1/FVC%. Reproduced with permission from Vijayan and Sankaran.[6]

Significance of lung function findings

These two cohort studies selected subjects based on clinical severity and, not surprisingly, found more marked physiological impairment over shorter periods of follow up. The picture which emerges in those with acute respiratory illness is of predominant airway injury with a less striking parenchymal effect, perhaps the residue of an acute interstitial injury. Although not followed for 10 years, these survivors show incomplete resolution of an initial acute lung injury. The very mild obstructive findings in the randomly selected general population at 10 years suggests a bronchiolar lesion in some of the exposed population, even in those without an immediate respiratory illness. Average values for lung function in an epidemiological study population can be misleading. A few severely abnormal individuals can produce the same average as a uniform but mild defect spread over the majority. Also, depending on sample size, quite severe defects in a small severely affected group who were either more heavily exposed or more susceptible to toxic injury may not be detected as a statistically significant effect of the exposure. It is worth noting that previous follow up studies of young cigarette smokers with abnormally low FEF_{25-75} values alone (normal FEV_1) showed no increased risk for disability or mortality compared with those with normal FEF_{25-75} values.

Because of a possible association of pre-existing reduced lung function with susceptibility to toxic injury and the association of lung disease from any cause with more symptoms and lower lung function, studies based on subjects identified by disease status rather than exposure status are susceptible to bias toward finding more severe pathophysiology. It is in this respect that the study by Cullinan *et al* is most illuminating, suggesting that the effects of brief exposure to methyl isocyanate (and, by extrapolation, other highly irritant gases) may persist for years after exposure.

The detection of a mild and persistent airway lesion is not surprising in view of animal studies initiated in the wake of Bhopal. It is, however, an unusual finding as community based follow up studies of less severe gas releases, such as the release of 50 tons of chlorine from a railroad tank car in 1978,[8] have not shown persisting defects as have studies of some smaller scale industrial releases affecting smaller groups of more intensely exposed workers.[9] It is significant that, among the long

LEARNING POINTS

* **A small study designed to provide a representative survey of all survivors of the Bhopal gas release conducted 10 years after the event found a higher prevalence of respiratory symptoms and lower mean mid expiratory flow rate associated with residence closer to the site of release.**
* **The study did not find lower FEV_1 (associated with risk for premature mortality) or evidence of airway hyperresponsiveness as measured by bronchodilator response to salbutamol.**
* **In relation to other follow up studies from the Bhopal incident, including those with acute respiratory illness, the toxic gas injury may be associated with a long standing macrophage alveolitis and symptoms in some of the most severely affected survivors.**
* **While the average defect in mid expiratory flow rate is modest, the persisting effect of a single gas exposure is noteworthy since such long standing effects from community wide events have not previously been documented.**
* **The extent of the Bhopal disaster was much more severe than most common, smaller scale industrial gas exposure events. Nonetheless, the findings, particularly if confirmed by further studies, suggest that major industrial accidents can produce both acute respiratory mortality and prolonged respiratory morbidity.**

term effects of a single massive industrial accident, residual lung damage may be found among the general population living downwind of the released gas. It shows how severe the exposure may need to be to produce a lasting effect on the respiratory system. It would be interesting to know whether defects in lung function among non-smokers without previous lung disease were found in individuals who were not acutely symptomatic at the time of the gas exposure.

Relationship to other studies of large scale gassings

Studies of the effects of inhalation of irritant gases began during the first World War when chlorine, sulphur-mustard, and phosgene were among gases used as chemical weapons. The pathologist Milton Winternitz performed detailed studies of the lungs of experimental animals quantitatively exposed to these gases[10] and drew attention to the presence of chronic lesions which persisted long after the acute injury had healed. However, although at that time Hutchinson's spirometer could have been used for epidemiological studies, appreciation of the need for measurement of respiratory physiology in relation to environmental exposure was not to come for many years. It was estimated that 100 000 soldiers died from gas inhalation and subsequent infectious complications in World War I. Assessments of the respiratory sequelae of war gas exposure in survivors were that "cases of recurrent bronchitis, bronchiectasis and emphysema . . . appeared to have a clear association with severe pulmonary effects at the time of gas exposure . . ." but that "the most significant observation was that the major proportion (of gas casualties evacuated to field medical units) exhibited complete recovery."[11] The idea that exposure to a single agent over a short period of time might produce clinically distinct outcomes—for example, bronchiolitis obliterans versus reactive airways disease—based on variations in exposure or individual susceptibility seems worthy of additional study. Sulphur-mustard gas victims from the Iran-Iraq War had a spectrum of pathologies including asthma, chronic bronchitis, bronchiectasis, airway narrowing due to scarring, and pulmonary fibrosis.[12]

An unanswered question

The prevalence of airway symptoms 10 years after exposure is higher than would be expected from the prevalence of mild airflow obstruction which, when present in young cigarette smokers, is usually asymptomatic. The disparity could be explained by the presence of non-obstructive chronic bronchitis affecting larger airways, or persistent hyperreactive airways from irritant injury (known variously as irritant asthma, asthma without latency, or reactive airways dysfunction syndrome). In an editorial accompanying the study of acutely affected patients by Vijayan and Sankaran, Nemery suggested the value of testing for non-specific bronchial hyperreactivity in follow up studies such as this.[13] Such tests would permit the detection of chronic airway hyperreactivity as a possible result of exposure to methyl isocyanate.

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