Sequential Respiratory, Psychologic, and Immunologic Studies in Relation to Methyl Isocyanate Exposure over Two Years with Model Development

S. R. Kamat, 1 M. H. Patel, 1 P. V. Pradhan, 1 Saroj P. Taskar, 1 Pratima R. Vaidya, 1 V. P. Kolhatkar, 1 J. P. Gopalani, 1 J. P. Chandarana, 1 Neepa Dalal, 1 and M. Naik 1

Of 113 methyl isocyanate (MIC)-exposed subjects studied initially at Bhopal, India, 79, 56, 68, and 87 were followed with clinical, lung function, radiographic, and immunologic tests at 3, 6, 12, 18, and 24 months. Though our cohort consisted of subjects at all ages showing a varied severity of initial illness, fewer females and young subjects were seen. Initially all had eye problems, but dominant symptoms were exertional dyspnea, cough, chest pain, sputum, and muscle weakness. A large number showed persistent depression mixed with anxiety, with disturbances of personality parameters. The early radiographic changes were lung edema, overinflation, enlarged heart, pleural scars, and consolidation. The persistent changes seen were interstitial deposits. Lung functions showed mainly restrictive changes with small airway obstruction; there was impairment of oxygen exchange. Oxygen exchange improved at 3-6 months, and spirometry improved at 12 months, only to decline later. The expiratory flow rates pertaining to large and medium airway function improved, but those for small airways remained low. There were changes of alveolitis in bronchoalveolar lavage fluid on fiber optic bronchoscopy, and in 11 cases positive MIC-specific antibodies to IgM, IgG, and IgE were demonstrated.

On follow up, only 48% of the subjects were clinically stable, while 50% showed fluctuations. Thirty-two percent of the subjects had lung function fluctuations. Detailed sequential behavior over 2-4 years was predicted for dyspnea, forced vital capacity, maximum expiratory flow rate (0.25-0.75), peak expiratory flow rate, VO2, and depression score. A model for clinical behavior explained a total variance of 52.4% by using the factors of cough, PCO2, and X-ray zones in addition to above five parameters. The behavior of the railway colony group (1640 patients) revealed a similar pattern of illness. When this observed pattern of changes was transferred to the affected Bhopal city sections (with an equitable age-sex distribution), our model results were again validated. Thus the picture of MIC-induced disease seems similar despite the differences for age-sex and initial severity of illness in our cohort and in the population of Bhopal city as predicted by our model.

Introduction

A leak of methyl isocyanate (MIC) from a 40-ton tank occurred in Bhopal, India, on December 2 and 3, 1984. Approximately 0.2 million residents were exposed to high concentrations (over 27 ppm) of MIC. As a result, it is believed that 2500 died within hours, about 3100 within a month, and 3289 over 4 years. In addition, in the first few days, many cattle, fowl, and other large animals also perished.

From direct scrutiny of records on the residents of the railway colony where the leak occurred, we determined that 30% of original victims might have persisting chronic disability. In this colony of 10,000, 135 died within 4 weeks, 1640 were treated by doctors, and 872 were admitted to hospitals.

Our study cohort consists of 113 subjects assessed within 3 months of exposure; initial findings have been published (1,2). Later we reported changes in flow rates and flow-volume (FV) loop up to 18 months (3) and immunologic changes (4); these results suggested that several victims developed weak, MIC-specific antibody titers in IgM, IgG, and IgE. We demonstrated patterns of inspiratory doming in the FV loop (3). Similar persistent abnormalities were demonstrated by guinea pigs by Alarie et al. (5).

To study the sequential behavior of MIC-exposed and persistently symptomatic subjects, we followed most of our cohort

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1Department of Respiratory Medicine and Psychiatry, Seth G. S. Medical College and K. E. M. Hospital, Bombay 400 012, India.
Address reprint requests to S. R. Kamat, Department of Respiratory Medicine and Psychiatry, Seth G. S. Medical College and K. E. M. Hospital, Bombay 400 012, India.
regularly for 2 years. We also developed a model on the basis of observed behavior for subjects in the railway colony and on Bhopal citizens of affected areas. This paper details our findings.

Materials and Methods

Persistently symptomatic residents of Bhopal (exposed to the MIC leak) who were seen at our hospital in Bombay within 7–90 days of the leak form the study cohort. Subjects were followed after 3, 6, 12, 18, and 24 months using a clinical respiratory questionnaire modeled on the BMRC (British Medical Research Council) questionnaire, which was used earlier in our work on occupational diseases (6).

In addition to physical examination, the following tests were conducted: chest radiography, spirometry (Stead Wells Spirometer, W. E. Collins, Boston, MA); bronchodilator tests with nebulized β2 stimulant aerosol; FV loop studies (Fleisch Pneumotachograph with Collin’s bodybox and Hewlett-Packard X-Y recorder; minute ventilation, oxygen uptake at rest and during submaximal exercise (with clinical end point at 4–5 min); and (at 0 and 3 months) arterial blood gases at rest and with exercise with carboxyhemoglobin (COHb) and methemoglobin (MetHb) (CO-oximeter and blood gas analyzer; Instrumentation Laboratories, Boston, MA). At later times COHb and MetHb were done only in selected abnormal subjects. Clinical grading of respiratory illness was done on the basis of the number and severity of symptoms; a score of 0–2 was considered mild, 3–4 moderate, and above 4 severe.

From the FV loop, we manually calculated gas flow (V) at 25, 50, and 75 %, peak expiratory flow rate (PEFR), and PIFR (inspiratory and expiratory flow) rates at respective phases and peak values. The transducers were calibrated before and after each reading, and an integrator was used for deriving the volume. Oxygen uptakes were calculated from volumes measured in a Douglas bag from the collected expired air. The chest radiographs were read together by two observers and classified as normal, emphysema, cardiovascular changes, or parenchymal and interstitial deposits. The latter were categorized as punctate, linear, micronodular, or reticular, along with their zonal distributions.

Serial observations at 3 months and later included psychiatric, psychosocial, and personality dysfunction in the cooperative group. In 12 subjects seriously ill at 1–3 months, we performed flexible fiber optic bronchoscopy with bronchoalveolar lavage. In eight subjects, lung biopsy was performed (five by needle and three open). From the moderately ill group, 52 ECGs and 32 RA tests and antinuclear factors were measured at the initial assessment. In a few cases with large broncho-reversibility, graded histamine airway hyperreactivity, lung volumes, and compliance were measured at 3 and 6 months. Immunologic studies (in collaboration with University of Pittsburgh, Pittsburgh, PA) with radioallergic (RAST) and MIC-specific antibodies were done in 99 subjects. These tests were done by preparing an antigen tagged with MIC to human serum albumin (MIC–HAS). Its efficacy and specificity were tested in guinea pigs, and antibody titers were measured by enzyme-linked immunoassay (ELISA) inhibition for IgG, IgM, and IgE. We also measured total IgE and RAST IgE with MIC–HAS (4).

Statistical analyses were done by Student’s t-tests, proportional chi-square tests, and, for antibody titers, by linear regression.

Model Development

After the initial analyses on the original cohort at 0 (n = 113), 3 (n = 79), 6 (n = 56), 12 (n = 68), 18 (n = 68), and 24 (n = 87) months by paired t-tests, we did intercorrelations by Pearson’s correlation coefficients at all phases separately and together. This helped us to identify significant variables to be used for evaluating sequential changes. To define changes in a more regular cohort (n=81; defined as those who attended at 0 and 24 months and at least once more), we substituted missing values with the average behavior and compared the individual behavior. The sequential behaviors in the original cohort, as actual patterns of 24 selected tests, were categorized as stable, improving, worsening, worsening after early improvement, and fluctuating. From these categories, we selected nine parameters for multifactorial regression (cough, dyspnea, forced vital capacity [FVC], PEFR, maximum expiratory flow rate [MEFR 0.25–0.75], Pco2, X-ray zones, Hamilton depression score, and oxygen up-take [Vo2]).

To account for differences of age–sex distribution between the original and regular cohort and between the railway colony patients and Bhopal city population, the following method was used: for both sexes and three age groups (0–19, 20–44, and 45 + years) numbers were calculated separately for actual proportions in each of the populations. From mean values of parameters in the cohort, a new mean value was derived. On the basis of initial known distribution in each group (as modified by age–sex), we assumed for later periods a worse transition probability for sequential changes. This was transferred to the new population; the progress was found to be similar in all age–sex groups. The originally selected (nine) variables were then subjected to multifactorial regression for all six phases, giving six Eigen values. From these two-factor composite equations we used the SPSS (Berkeley, CA) program to derive two-factor scores and severity scores for close–factor analyses. We obtained Eigen values and derived variance to explain the cohort behavior by this method.

Results

Table 1 lists the sex–age distribution of the original cohort studied at our institute. If the distance of exposure from the gas leak was greater, there was a greater chance of initial clinical illness being mild. A slightly greater proportion of severe cases in our cohort were seen as compared to the cases treated in the railway colony. (See below; two-thirds of our cohort came from this group.) In comparison with the initial clinical severity of illness, when we assessed the cases at our institute, 69 % had improved, 4 % had worsened, and the rest were unchanged.

Table 2 lists the sequential patterns in clinical symptoms under three categories. With six assessments done over 2 years on this cohort, we restudied 68 at 12 months and 87 at 24 months. The frequency (percent) of chest symptoms is listed as neurologic or psychosomatic as assessed by qualified psychiatrists. Psychiatric testing was not done at the first stage as the subjects were very ill and it was perhaps cruel to do prolonged testing immediately after the tragedy; the tests were also not possible due to not obtaining cooperation in a proportion of cases.

Respiratory symptoms scores decreased at 3, 6, and 12 months but increased significantly later. The commonest symptom was
testing was done at the first stage as the subjects were very ill and it was perhaps cruel to do prolonged testing immediately after the tragedy; the tests were also not possible due to not obtaining cooperation in a proportion of cases.

Respiratory symptoms scores decreased at 3, 6, and 12 months but increased significantly later. The commonest symptom was dyspnea on exertion; a paroxysmal component was unusual. These subjects were intermittently given antibiotics and bronchodilators by local doctors, but despite this, the symptoms persisted. From neurologic symptoms spontaneously elicited, muscle weakness and poor memory became more frequent (0.05). The eye problems (which were subsequently present in 2–10%) and abdominal symptoms (seem unrelated) are not listed. Several more symptoms were diagnosed by a psychiatrist. Perhaps some of these were related to procedures in the protracted legal compensation case.

Table 3 lists the psychiatric abnormalities as assessed by psychiatrists and social workers. Table 3 shows that only 19–27% were considered normal. The proportions with pure anxiety or depression increased over 2 years but those with mixed lesions decreased (p < 0.05). Hamilton scoring revealed that the proportions with normal scores for both anxiety and depression declined over 2 years (p<0.05).

| Table 1. Age-sex distribution of 113 MIC-exposed subjects and severity of illness: original cohort. |
|---------------------------------------------------------------|
| Sex | Total (%) | Age, years | <20 | 21-40 | 41-50 | <50 |
|-----------------|------------|-------------|-----|--------|--------|-----|
| Male | 87 (77%) | 4 | 38 | 28 | 17 |
| Female | 26 (23%) | 6 | 19 | 1 | — |

| Clinical | | | Mild | Moderate | Severe |
|-----------------|-------------|--------|--------|---------|--------|
| symptom | | | 30 (27%) | 57 (50%) | 26 (23%) |

| Table 2. Sequential patterns in clinical symptoms in the original cohort. |
|---------------------------------------------------------------|
| Symptom | Month (r) | Neurologic, % |
|-----------------|------------|-------------|
| Respiration, % | Respiratory score | 29 |
| Cough | 2.92 | 32 |
| Sputum | 2.53 | 32 |
| Dyspnea | 2.32 | 29 |
| Chest pain | 2.05 | 25 |
| Respiratory score | 2.82 | 25 |
| ± SD | 1.55 | 15 |
| Body ache | 1.34* | 32 |
| Muscle weakness | 1.17* | 32 |
| Poor memory | 1.13* | 32 |
| Poor concentration | 1.20 | 32 |
| Tremors | 1.27 | 32 |
| Psychiatrist's assessment number, % | 32 | 58 |
| Body ache | 8 | 35 |
| Insomnia | 32 | 42 |
| Headache | 29 | 42 |
| Joint pains | 16 | 30 |
| Apathy | 16 | 12 |
| Tiredness | 19 | 12 |
| Giddiness | 14 | 25 |

*Significantly improved, p < 0.05

| Table 3. Patterns in psychiatric abnormalities. |
|------------------------------------------------|
| Symptom | Month |
|-----------------|--------|
| Psychiatric assessment | 3 | 6 | 12 | 18 | 24 |
| No. studied | 60 | 37 | 42 | 63 | 60 |
| Normal, % | 23.3 | 27 | 26.2 | 19 | 20 |
| Anxiety, % | 8.3* | 5.4 | 11.9 | 25.4* | 15 |
| Depression, % | 15* | 27 | 21.4 | 19 | 36.7* |
| Mixed, % | 53.3* | 40.5 | 40.5 | 36.5 | 28.3* |
| Grading by Hamilton scores | 3 | 6 | 12 | 18 | 24 |
| No. studied | 48 | 36 | 36 | 48 | 60 |
| Anxiety, % | 45.8* | 38.8 | 27.7 | 22.9* | 26.6* |
| Mild (13-24) | 20.8 | 22.2 | 19.4 | 52.1 | 34.4 |
| Moderate (25-36) | 33.3 | 27.7 | 47.2 | 22.9 | 28.1 |
| Severe (36+) | 0 | 11.1 | 5.5 | 21.1 | 10.9 |
| Depression, % | 65.3* | 51.4 | 37.4 | 45.8* | 46 |
| None (1-12) | 24.5* | 21.6 | 13.5 | 33.3 | 34.6* |
| Mild (16-25) | 6.1 | 21.6 | 37.8 | 16.7 | 12.7 |
| Moderate (26-35) | 4.1 | 5.4 | 10.8 | 4.2 | 6.3 |

*Significant at p < 0.05.

Those with mild abnormalities simultaneously increased. These assessments also covered memory count, I.Q. assessment, and Bender–Gestalt scores. For the latter two scores, the proportions with normal scores increased significantly after 12 months (p<0.05), while for memory count there was no improvement.

Table 4 reports results of personality dysfunction and psychosocial studies that were obtained after filling a detailed proforma and checking. The results show a large prevalence of post-MIC exposure abnormalities. In six categories there was significant partial improvement, best seen at 18 months. Table 4 lists increased prevalences of abnormal psychosocial function after

| Table 4. Sequential patterns in personality and psychosocial function in MIC-exposed subjects. |
|---------------------------------------------------------------|
| Assessment | Month |
|-----------------|--------|
| Personality dysfunction, abnormal %* | 3 | 6 | 12 | 18 | 24 |
| No. studied | 60 | 59 | 72 | 69 | 65 |
| Irritability | 75 | 70 | 72 | 58 | 64 |
| Poor concentration | 70 | 56 | 67 | 45* | 52 |
| Indecisive | 60 | 46 | 51 | 32* | 45 |
| Poor adjustment | 52 | 51 | 47 | 26* | 25* |
| Unstable relationship | 50 | 46 | 53 | 36 | 40 |
| Emotional lability | 45 | 26 | 15 | 2* | — |
| Overdependent | 40 | 42 | 33 | 35 | 46 |
| Hypersensitive | 68 | 49 | 47 | 38* | 48 |
| Cannot cope with frustration | 75 | 61 | 72 | 55* | 60 |
| Psychosocial function, abnormal relationship, % (pre-MIC, n=91)† | 3 | 6 | 12 | 18 | 24 |
| Family | 4 | 62 | 59 | 62 | 44 |
| Interpersonal | 4 | 67 | 49 | 46 | 20 |
| Social | 0 | 58 | 54 | 50 | 49 |
| Job | 12 | 70 | 73 | 78 | 61 |
| Marital | 5 | 17 | 26 | 29* | 18 |
| Sexual | 1 | 67 | 41 | 55* | 54 |

*These assessments were not done in some subjects who were not cooperative.
†Omitted in some subjects (up to 10) as not applicable.
‡Pre-exposure status assessed as generally better.
§Significant improvement compared to 3-month status (p<0.05).
¶Pre-MIC and all post-MIC status differences, p<0.01 except marital; p<0.05. Total psychosocial status at 3 months and 12 months correlated significantly to FVC (p<0.01; r = 0.51 and 0.77, respectively) and FEV, (p<0.01; r = 0.56 and 0.73, respectively).
significant partial improvement, best seen at 18 months. Table 4 lists increased prevalences of abnormal psychosocial function after MIC exposure. Some assessments were omitted in a few subjects, where considered not applicable (e.g., job, marital). The total abnormality score at 3 and 12 months correlated significantly to FVC and FEV1 (forced expiratory volume in 1 sec), suggesting that these abnormalities were a consequence of lung functional disability. These persistent psychologic abnormalities may be secondary to organic lung disease.

**Radiographic and Lung Function Changes**

Table 5 lists chest radiographic patterns. Only 2–4% of films over 2 years were read as normal by our criteria. The proportions having overinflation, pleural scars, heart enlargement, and consolidation declined by 6 months and later (p < 0.05). At the early stage, only in a few, consolidations responded to antibiotics and in one case distinct calcified scars developed at the right base. However, the main changes seen were interstitial shadows, which were distributed in fewer zones after 12 months; but generally 3–4 zones were involved with linear or punctate deposits. The punctate deposits were seen less often at 18 and 24 months, and micronodular infiltrates decreased at 12 months or later (p < 0.05 for both).

Table 6 lists the mean trends in lung function and blood gases. While at 0 and 3 months, all subjects cooperated with blood gas studies, at later periods (not done at 6 months) we restricted these to more abnormal subjects. Oxygen uptake at rest did not show further change after 3 months (Table 6).

Exercise VO2 increased adequately at 3 months, and the improvement was maintained (paired comparison in 44 subjects: 1123 ± 280 mL at 0, 1157 ± 403 mL at 3 months, p < 0.05). Initially PO2 dropped significantly with exercise in 39% subjects. PO2 at rest did not change significantly, but PCO2 rose at 24 months (p < 0.05), and pH declined between 12 and 24 months (p < 0.05); COHb and MetHb decreased to near normal levels by 3 months (p < 0.05). There was no relationship of these values to the initial clinical severity.

Table 6 lists lung functions as true values. If these are evaluated as standardized (to age, height, and sex) and compared statistically, the conclusions remain similar. Also, if one restricts the analyses to a common group, the trends seen are unchanged (it seemed that more improved cases defaulted easily). Thus, FVC and FEV1 improved by 12 months, then declined later. The PEFR values increased by 12 months and later maintained improvement. MEFR (0.25–0.75) values did not improve, nor did MEFR (200–1200). There was a significant reduction of FEV1/FVC% by 12 months that persisted. Significant bronchodilator response was seen in a small proportion, which did not seem to accentuate later. Initially only 11.6% showed an improvement in FEV1, between II and 20%) and in 8.9% it was above 20%. At 3 months, the respective proportions were 7.7 and 8.8%. Thus, there seems

### Table 5. Serial radiographic patterns in the MIC-exposed (n = 113) cohort.

| Pattern                      | Month (n)                     | 0 (113) | 3 (79) | 6 (56) | 12 (68) | 18 (68) | 24 (87) |
|------------------------------|-------------------------------|---------|--------|--------|---------|---------|---------|
| Normal, %                    |                               | 2       | 2      | 2      | 4       | 0       | 0       |
| General abnormalities        |                               | 0       | 3      | 7      |         |         |         |
| Overinflation                |                               | 15      | 7      | 14     | 0       | 5       | 7       |
| Pleural scars                |                               | 21      | 3      | 10     | 0       | 2       | 6       |
| Consolidation                |                               | 4       | 6      | 0      | 0       | 0       | 1       |
| Enlarged heart               |                               | 19      | 3      | 4      | 2       | 3       | 5       |
| Parenchymal scars            |                               | 3       | 6      | 6      | 4       | 3       | 3       |
| Interstitial deposits zonal distribution |                   | 1–2     | 36     | 25     | 24      | 9       | 36      |
| 3–4                          |                               | 40      | 49     | 48     | 64      | 59      | 51      |
| 5–6                          |                               | 24*     | 26     | 24     | 27      | 5*      | 20      |
| Type                         |                               | 82      | 64     | 86     | 92      | 94      | 94      |
| Linear                       |                               | 37      | 43     | 28     | 58      | 20*     | 16*     |
| Reticular                    |                               | 27      | 6      | 16     | 14      | 23      | 24      |
| Micronodular                 |                               | 27      | 32     | 36     | 14*     | 3*      | 8*      |
| Change from 0 months         |                               | —       | 66     | 66     | 62      | 67      | 58      |
| Worse                        |                               | —       | 6      | 20     | 11      | 10      | 12      |

*p < 0.05

### Table 6. Sequential lung function trends in MIC-exposed (n = 113) cohort.

| Measurement          | 0 (113) | 3 (79) | 6 (56) | 12 (68) | 18 (68) | 24 (87) |
|----------------------|---------|--------|--------|---------|---------|---------|
| FVC, L (L)           | 2.05 ± 0.68 | 2.08 ± 0.62 | 1.99 ± 0.58 | 2.68 ± 0.66* | 2.91 ± 0.68 | 2.59 ± 0.66 |
| FEV1, L (%)          | 1.98 ± 0.67 | 1.97 ± 0.62 | 1.93 ± 0.57 | 2.24 ± 0.60* | 2.26 ± 0.59 | 2.14 ± 0.62 |
| VC, observed/predicted | 70.3 ± 16.9 | 70.1 | 67.3 | 93.3 | 99.9 | 87.9 |
| PEFR, L (%)          | 362.3 ± 128 | 403 ± 123 | 412 ± 100 | 444 ± 105 | 469 ± 90* | 467 ± 106 |
| FEV1/FVC%            | 97 ± 4*     | 96 ± 5 | 97 ± 6 | 83 ± 8*     | 79 ± 9 | 83 ± 10 |
| Bronchodreversibility |          |        |        |          |         |         |
| FEV1, % increase     | 7.2 ± 10.2* | 4.8 ± 8.1* | 5.1 ± 5.9* | 5.4 ± 7.5* | 3.8 ± 5.3* | 5.8 ± 8.9* |
| MEFR 0.25–0.75 L/min | 200 ± 82 | 213 ± 93 | 207 ± 70 | 170 ± 79 | 144 ± 76 | 150 ± 72 |
| MEFR 0.20–1.00 L/min | 234 ± 112 | 256 ± 116 | 249 ± 96 | 265 ± 109 | 272 ± 109 | 241 ± 118 |
| Gas exchange         |          |        |        |          |         |         |
| MV, L (L)            | 8.45 ± 3.27 | 9.45 ± 2.44 | 10.29 ± 1.84 | 9.96 ± 2.16 | 10.45 ± 1.49 | 8.94 ± 2.54 |
| VD, L (L)            | 198 ± 59* | 227 ± 50* | 218 ± 52 | 236 ± 45 | 243 ± 43 | 244 ± 102 |
| PO2 mm Hg (n)        | 100.9 ± 12.8 | 88.8 ± 20.3 | — | 94.1 ± 12.4 | 93.8 ± 10.6 | 94.9 ± 9.8 (16) |
| PCO2 mm Hg           | 33.3 ± 3.7* | 33.3 ± 4.6 | — | 33.6 ± 3.1 | 34.1 ± 1.4 | 38.2 ± 4* |
| pH                   | 7.49 ± 0.05* | 7.46 ± 0.06* | — | 7.43 ± 0.04* | 7.42 ± 0.04 | 7.39 ± 0.03* |
| COHb (g/dL)          | 5.97 ± 11.1* | 2.28 ± 1.43* | 51* | 2.26 ± 1.48 | 2.29 ± 1.29 | 2.28 ± 1.48 |
| MetHb (g/dL)         | 1.76 ± 0.74* | 0.88 ± 0.73* | — | 0.66 ± 0.27 | 0.40 ± 0.27 | 0.38 ± 0.17 |

*Significantly different from controls, p < 0.05.
†Significantly lower, p < 0.05.

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; VC, vital capacity; PEFR, peak expiratory flow rate; MEFR, maximum expiratory flow; MEFR, maximum expiratory flow rate; MV, minute ventilation; COHb, carboxyhemoglobin; MetHb, methemoglobin.

*Similar results if age, height, and sex are standardized.

*p < 0.05.
to be no increase in "asthmatic" tendency after MIC exposure. In 10 cases tested for graded histamine airway reactivity (0.03–16 mg/mL concentration) at 3 and 6 months using standard techniques, 5 reacted at 1 mg/mL concentration (PC20 [provocative concentration: 20% decrease in FEV₁]) while 3 showed PC20 at 5 mg/mL. The changes in DMBC (direct maximal
breathing capacity), RR (respiratory rate), or MV (minute ventilation) were insignificant. In four cases with severe disability, there were no abnormalities of response to graded hypoxia.

When the initial FVC and FEV₁ were correlated to respiratory symptom scores, there was a very significant relationship (FVC: \( r = -0.76; \) FEV₁: \( r = -0.79; \) postbronchodilator FEV₁: \( r = -0.85 \)). Thus we concluded that our clinical symptomatology was reflected in the functional values measured.

**Pathologic and Immunologic Results**

Pathology and immunology are reported in detail elsewhere (2,4). Lung histology in closed needle (\( n = 5 \)) biopsies showed collagenous tissue. In three open biopsies, mild septal and pleural fibrosis, perivascular, and peribronchial fibrosis, active bronchitis, inflammatory interstitial exudate, distended bronchioles filled with mucinous material with interstitial scarring, and muscular-thickened vessels were seen. (Figs. 1 and 2).

Fiberoptic bronchoscopy findings (2) (done within 4 weeks) showed distorted airway lumen and mucosal swelling in all, lymphoid hyperplasia in 3, ulceration in 2, and patchy congestion in 3. Bronchoalveolar lavage (BAL) done in 14 cases showed high total cell count in all with neutrophil excess (\( n = 9 \)), macrophage increase (\( n = 2 \)), eosinophil excess (\( n = 1 \)) and lymphocytosis (\( n = 1 \)).

Immunologic studies done in 99 subjects collected at intervals are shown in Table 7. Total IgE levels showed insignificantly high levels initially, which later declined. Preliminary studies proved that antibodies specific to MIC (as GSA or HSA) were detected by ELISA inhibition assays, and these did not cross-react to other isocyanates or conjugates. Thus, MIC–KLH was shown to inhibit antibody specific to MIC. Upon storage, the sera, due to lag from delay in sending samples to United States, did not decay (which may have affected their evaluation). Mean RAST IgE binding revealed levels from 2.31 ± 2.95% (10 months) to 3.68 ± 4.95% (12 months). While these were related closely to total IgE levels values, both were unrelated to clinical or functional changes seen. In 11 cases, MIC-specific antibodies were detected (IgM; 7, IgE; 4; IgG, 6) on several occasions. In one case antibodies were detected 1 year after exposure, but in most subjects, these were found in a sample taken within 3 months. In 10 subjects with clinically adequate data, 4 had severe and 6 had moderate initial illness. Radiographically, one to three zones showed interstitial deposits in three subjects and four to six zones in seven cases. It appeared that those ill initially but who improved later developed positive antibodies. This finding of MIC–specific positive antibodies, albeit with low titers, has crucial medical and legal significance for a cause–effect relationship.

| Table 7. Immunologic results in MIC-exposed (\( n = 99 \)) subjects. |
|--------------------|---|---|---|---|---|---|
| Measurement       | 0 (63) | 3 (79) | 6 (66) | 12 (96) | 18 (25) | 24 (17) |
| Total IgE, IU     | 1230±7 | 1141±6 | 711±4 | 618±4 | 973±7 | 678±6 |
| RAST binding, IU  | 2.31±3 | 2.23±3 | 2.74±3 | 3.68±3 | — | — |
| IgE               | 2.95  | 2.65  | 3.07  | 4.95  | — | — |
| Control, IgE (n)  | 424±4 | 305±4 | 1016±39 | 1006±39 | — | — |

*Measurements restricted to abnormalities.

**Table 8. Graphic trends in MIC-exposed subjects (\( n = 113 \)) with acceptable patterns.**

| Parameters \( a \) | Stable | Improving | Worsening | Improving and then worsening | Fluctuating |
|---------------------|--------|-----------|-----------|-------------------------------|------------|
| Clinical dyspnoea (93) | 45(48.4) | 22(23.7) | 7(7.5) | 9(9.9) | 20(22.0) |
| Cough (90) | 16(17.8) | 8(8.9) | 13(14.4) | 8(8.9) | 45(50) |
| Sputum (91) | 2(2.3) | 14(15.4) | 11(12.1) | 10(11) | 35(38.5) |
| Lung (92) | 35(38.0) | 26(28.3) | 6(6.5) | 0 | 17(18.5) |
| X-ray signs (92) | 5(5.5) | 19(20.9) | 19(20.9) | 13(14.3) | 35(38.5) |
| Lung function | 13(14.1) | 26(28.3) | 0 | 22(23.9) | 31(33.7) |
| FEV₁ (91) | 3(3.41) | 26(28.6) | 1(1.1) | 14(15.4) | 19(20.9) |
| Bronchoconstriction, FEV₁ (85) | 74(87.1) | 4(4.7) | 7(8.2) | 1(1.2) | — |
| MEFR (14.8) | 5(5.7) | 37(42.1) | 18(20.4) | 15(17.1) | — |
| MEFR (0.5-0.75) (88) | 17(18.7) | 9(9.4) | 17(18.7) | 29(31.9) | — |

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 sec; MEFR, maximum expiratory flow rate; PEFR, peak expiratory flow rate; MV, minute ventilation; COHb, carboxyhemoglobin; MetHb, methemoglobin.

*Total number in parentheses.

**Defaults and Relationship to Clinical and Functional Sequence**

Though we had planned a full follow-up for 2 years in six phases, we did not succeed fully. At 1 and 2 years, we followed 68 and 87 subjects. Of these, those who were assessed functionally and clinically on at least two subsequent occasions (including the last) were included in the regular (81) cohort. When these were compared, it was seen that defaulters (32) were slightly less abnormal initially and improved more. On preliminary analysis, it was seen that while many showed improvement up to 12 months and deteriorated later, there were other patterns, e.g.,

| Table 9. Mean trends in lung function in the regular cohort (\( n = 81 \)).* |
|-----------------|-----|-----|-----|-----|-----|
| Measurement     | 0(81) | 3(69) | 6(55) | 12(69) | 18(65) | 24(81) |
| FVC, L          | 2.02 | 2.02 | 1.96 | 2.66 | 2.84 | 2.59 |
| FEV₁, L         | 1.93 | 1.95 | 1.91 | 2.23 | 2.26 | 2.14 |
| FEV₁/FVC, %     | 95.5 | 96.1 | 75.2 | 83.1 | 79.8 | 82.3 |
| Bronchoconstriction, % | 5.7 | 5.9 | 5.1 | 5.5 | 3.8 | 5.8 |
| MEFR (0.25-0.75), L/min | 194 | 230 | 204 | 168 | 144 | 147 |
| PEFR, L/min     | 363 | 400 | 410 | 445 | 471 | 466 |
| MV, L/min       | 8.35 | 9.52 | 10.31 | 10.02 | 10.46 | 8.85 |
| PO₂, mm         | 80.4 | 93 | 94.1 | 93.8 | 94.1 | 94.1 |
| Pco₂, mm        | 33.5 | 31 | 33.5 | 34.1 | 38.3 | — |
| pH              | 7.49 | 7.47 | — | 7.43 | 7.39 | 7.38 |

*SDs omitted as they were similar to those listed in Table 7.
stable, improving, worsening, fluctuating, and improvement followed by deterioration. The general behavior was that 25–30% were constantly improving and one-half belonged to the last category.

We decided to look at this problem in detail for 15 parameters. In those where follow-up data showed a clear trend, we graphically derived their patterns individually; the results are shown in Table 8. It is seen that all parameters do not change identically, e.g., cough and dyspnea show different trends, as do FVC, PEF, and MEFR (0.25–0.75). The trends for COHb and MetHb showed only large improvements. For developing a model, we thought this to be a good primary step. A fluctuating behavior was seen in 20–50% of subjects in various parameters (we did not analyze changes in bodybox or flow–volume loop values as we had not done these tests initially in many subjects).

Results in Regular Cohort

The results in the regular cohort (n = 81) are presented in Tables 9 and 10. Table 9 shows that despite the data being restricted to 81 cases, the trends for various parameters are similar; the significance of differences are also the same. Table 10 gives results for depression, anxiety scores, and IgE. Again the changes are similar to those in the original cohort.

When distribution of clinical chest symptoms and signs are compared in six phases along with severity of initial clinical

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**Table 10. Sequential trends for anxiety, depression, and IgE levels in the regular cohort (n = 81).**

| Hamilton scores | Month (n) | 3 (50) | 6 (43) | 12 (50) | 18 (40) | 24 (58) |
|----------------|-----------|--------|--------|---------|---------|---------|
| Anxiety        |           | 15.3   | 19.5   | 19.6    | 19.1    | 20.1    |
| Depression     | b          | 12.1   | 15.6   | 16.5    | 17.2    | 14.3    | 16.3    |
| IgE units      |           | 1355   | 950    | 789     | 648     |

*SDs similar to values for the cohort in Table 6.

b n = 48 at 0 months.

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**Table 11. Correlation coefficients in the total cohort at the initial stage.**

|              | Cough | Sputum | Dyspnea | FVC    | FEV1   | MEF25  | MEF20-1200 | PEF    | Vo2   | DMBC  |
|--------------|-------|--------|---------|--------|--------|--------|------------|--------|-------|-------|
| Sputum       | 0.52* | -      | 0.39*   | -0.22  | -0.26* | -0.24* | -0.25      | -0.21  | -     |       |
| Dyspnea      | 0.29* | -      | -0.16   | -0.16  | -0.16  | -0.15  | -0.13      | -0.13  | -     |       |
| Weight       | -     | -      | -0.27*  | -0.27* | -0.22  | -0.33  | 0.41*      | 0.27*  | -     |       |
| Lung signs   | 0.27* | -      | -0.26   | -       | -      | -       | -          | -      | -     |       |
| Cough        | -     | -      | 0.26*   | -0.30* | -      | -       | -          | -      | -     |       |
| FVC          | -     | 0.98*  | 0.81*   | 0.81   | 0.80*  | 0.33*  | 0.88*      |        |       |
| FEV1         |       | -      | 0.85*   | 0.83   | 0.82*  | 0.32*  | 0.92*      |        |       |
| MetHb        |       |        | -0.26*  | -       | -0.26* | -       | -          | -      | -     |       |
| Po2          | -     | -      | -0.28*  | -       | -      | -       | -          | -      | -     |       |
| Vo2          | -     | -      | -0.29*  | -       | -0.38* | -       | -          | -      | -     |       |
| Reversibility| -     | -      | -0.40*  | -       | -      | -       | -          | -      | -     |       |
| MV           | -     | -      | 0.74*   | -       | -      | -       | -          | -      | -     |       |

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; MetHb, methemoglobin; MV, minute ventilation; MEF, maximum expiratory flow; PEF, peak expiratory flow rate; DMBC, direct maximal breathing capacity.

*p < 0.05

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**Table 12. Correlation coefficients in the total cohort covering six phases over 2 years.**

|              | FVC    | MV     | IgE    | FEV1   | MEF25  | MetHb | CoHb   | Cough  | Dyspnea | Lung signs | Weight | Sputum | X-ray |
|--------------|--------|--------|--------|--------|--------|-------|--------|--------|---------|------------|--------|--------|-------|
| Sputum       |        | -      | -      | -      | -      | -     | -      | 0.58*  | 0.26*   | 0.17      | -      | -      | -     |
| Dyspnea      |        | -      | -      | -      | -      | -     | -      | 0.19   | -       | -0.21     | -      | -      | -     |
| Lung signs   |        | -      | -      | -      | -      | -     | -      | 0.19   | -       | -0.17     | -      | -      | -     |
| FVC          |        | -      | -      | -      | -      | -     | -      | 0.22   | -0.26   | -0.21     | -      | -      | -     |
| FEV1         |        | -      | -      | -      | -      | -     | -      | 0.17   | 0.31    | 0.23      | -      | -      | -     |
| MetHb        |        | -      | -      | -      | -      | -     | -      | 0.16   | 0.19    | 0.15      | -      | -      | -     |
| Lung over-inflated | 0.16* | -      | -      | -      | -      | -     | -      | -      | -       | -0.20     | -      | -      | -     |
| COHb         |        | -      | -      | -      | -      | -     | -      | 0.27   | 0.28    | -0.20     | -      | -      | -     |
| MetHb        |        | -      | -      | -      | -      | -     | -      | 0.18   | 0.19    | 0.19      | -      | -      | -     |
| Po2          |        | -      | -      | -      | -      | -     | -      | 0.29   | 0.12    | -0.29     | -      | -      | -     |
| PCO2         | 0.37*  | -      | -      | -      | -      | -     | -      | 0.45   | 0.23    | -0.26     | -      | -      | -     |
| pH           |        | -      | -      | -      | -      | -     | -      | 0.18   | 0.19    | 0.19      | -      | -      | -     |
| MEF200       |        | -      | -      | -      | -      | -     | -      | 0.26*  | -       | -0.14     | -      | -      | -     |
| DMBC         |        | -      | -      | -      | -      | -     | -      | 0.29   | 0.12    | -0.29     | -      | -      | -     |
| MV           |        | -      | -      | -      | -      | -     | -      | 0.14*  | -       | -0.36     | -      | -      | -     |
| Vo2          | 0.22*  | 0.63*  | -      | -      | -      | -     | -      | 0.24   | 0.19    | -0.36     | -      | -      | -     |
| Depression   | 0.22*  | -      | -      | -      | -      | -     | -      | 0.26   | 0.28    | 0.17      | -      | -      | -     |
| Anxiety      | 0.18*  | -      | -      | -      | -      | -     | -      | 0.25   | 0.31    | 0.16      | -      | -      | -     |
| PEF          | -      | 0.14*  | -      | -      | -      | -     | -      | 0.13   | 0.34    | -0.26     | -      | -      | -     |
| Reversibility| 0.20*  | -      | -      | -      | -      | -     | -      | -      | -       | -0.30     | -      | -      | -     |
| IgE          |        | -      | -      | -      | -      | -     | -      | 0.18   | 0.18    | -0.30     | -      | -      | -     |

Abbreviations: FVC, forced vital capacity; MV, minute ventilation; FEV1, forced expiratory capacity in 1 sec; MEF, maximum expiratory flow; MetHb, methemoglobin; CoHb, carboxyhemoglobin; DMBC, direct maximal breathing capacity; PEF, peak expiratory flow.

*p < 0.005

*p < 0.001
illness (not tabulated), the trends are similar to the total cohort. More older females suffered greater illness initially, but later the behavior in both sexes was similar. Therefore, we worked out trends in correlation coefficients (as a guide to regression analyses) on the total cohort. These were worked out on all possible parameters in six phases individually and together, but results on more significant values covering all phases are listed in Tables 11 and 12.

**Intercorrelation over Two Years**

Functional parameters were closely interrelated. At the initial stage (Table 11), cough, sputum, and dyspnea are moderately interrelated, along with abnormal lung signs (but not overinflation). Sputum is significantly related to FEV₁, MEFR (0.25–0.75), and MEFR (200–1200). Dyspnea, however, is not significantly correlated to lung functions, but cough is correlated to FEV₁ and MEFR (200–1200). Lung signs correlated to FVC and FEV₁, while MetHb correlated to MEFR (0.25–0.75) and PEFR and Po₂ to MEFR (0.25–0.75).

Table 12 correlates the coefficients covering all six phases. Due to larger volumes of data, several more correlates now seem significant. Thus, chest symptoms and signs are interrelated, as are lung functions, blood gases, DMBC, VO₂, scores for anxiety and depression. IgE levels correlated to MetHb values.

From these results we concentrated on the following parameters in modeling for a sequential behaviour in the regular cohort: a) clinical: cough, dyspnea; b) function: FVC, MEFR (0.25–0.75), PEFR, VO₂, PCO₂; c) X-ray zones and depression score.

Figures 3–8 delineate the types of patterns on six selected parameters on the regular cohort as homogenized curves extending beyond 24 months. Thus, if an individual’s progress is known during the first 24 months by actual (at least three) observations, his future course can be predicted by our graphic display. Table 13 also gives the actual proportions on each of the six parameters. For dyspnea, there were four patterns with 45.7% as stable (Fig. 3). For FVC, the major pattern (of four) was fluctuating (35.8%), for MEFR (0.25–0.75), the major pattern (of five) seen was worsening (40.7%), followed by worsening after early improvement (24.7%) (VE75 [expiratory flow at 75% of VC]) from FV loop tends to behave similarly). For PEFR, the main pattern was improvement (53.1%) (as also for VO₂, 39.5%). For depression score, the main pattern was fluctuating. Thus, on the regular cohort we predicted changes in six parameters fairly accurately.

Table 14 shows the further development of this concept by doing multifactorial analyses. Analyses were conducted on seven parameters listed for factor 1 at all six phases and later only for the first and sixth phases. Thus, as step 1, six (Eigen value) equations were derived and at step 2 factor scores as listed in Table 14 were derived. Corresponding factor scores for six variables with large values in the first equation and smaller ones in the second equation were worked out. Then the factorial score for two factors and severity scores were obtained, accounting for variance. Eigen values for two sets of variables were derived. When FVC, MEFR (0.25–0.75), and PEFR, which are closely related, are accounted for in the first effort, correlation with cough, dyspnea, PCO₂, and X-ray zone become significant (Table 14). By variance analyses in these two attempts we could explain a variance of 36.5 and 15.9%, respectively (Table 14).

Thus, using seven parameters, our model could explain behavior of 52.4% (a model with moderate accuracy). If one correlated the clinical severity, the model prediction is significantly correlated (p < 0.01). We validated our model by working on the other four phases. As the behavior over 2 years of MIC-exposed cases was not different by age/sex, we thought this multifactorial model could be applied to other cohorts or Bhopal city population also.

Table 15 describes these attempts to transfer this behavior to the railway colony cohort. It describes the age–sex distribution according to the severity of initial clinical illness seen from the actual records of treated cases scrutinized and classified by the senior author. A total of 1640 subjects were treated, and in 1617 cases, data were adequate for such classification. Table 15 reveals

![Figure 3](image1.png)

**Figure 3.** Patterns observed for breathlessness (grades) on vertical axis and time interval in months on horizontal axis. The actual proportions are given in Table 13. The curves are homogenized and projected beyond 24 months of actual observation.

![Figure 4](image2.png)

**Figure 4.** Similar patterns of forced vital capacity shown in milliliters on vertical axis for the month of measurement. Note that the behavior is different from that in Figure 1.
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1. Patterns for maximum expiratory flow rate (0.25–0.75) shown as liters/minute on the vertical axis for the month of measurement. The improving group also shows only a small increase.

2. Patterns for peak expiratory flow rate shown as liters/minute on the vertical axis for month of measurement. Generally, all groups show some improvement.

3. Patterns for O₂ uptake shown as milliliters/minute on the vertical axis for month of measurement. There are many variations.

4. Patterns of Hamilton depression scores. Each of these parameters seem to have peculiar variations.

In the railway colony cohort, there are a greater number of younger subjects and more females, along with an excess of mildly affected cases. On comparison for these behaviors, in this population and our regular cohort, we found no statistical differences. The differences we looked for were the clinical, functional, and psychologic parameters.

Table 16 gives additional data on age, sex, types of clinical initial symptoms, and severity of illness. The admitted group consisted of a larger proportion of moderate and seriously ill cases. In a large majority, the initial illness lasted up to 2 weeks and in 30.3% it persisted to become chronic. In those admitted, the illness, perhaps due to treatment, seemed to have remitted more often.

Table 17 details results by applying our factorial model to predict in three severity categories the clinical behavior for 2 years on the railway colony cohort. At 0 months, older subjects had more severe illnesses. The proportion in the mild category increased later, particularly at younger ages. But for all ages, the moderate category predominates in later periods, particularly at older ages. This means that after some improvement (which was greater in younger subjects), there is enhancement of symptoms and their severity over 2 years.

Table 18 projects age-standardized (to account for any differences) sequential behavior of four functional parameters and depression as per our model on the railway colony cohort. Behavior is similar to our regular cohort and broadly shows a fluctuating course; for FVC, maximal improvement in all three groups is seen at 18 months (irrespective of initial severity). For MEFR (0.25–0.75), there is a gradual reduction over 24 months to a level that is slightly lower in the severe group at 24 months (though differences are large initially). For PEFR, the trends are similar to FVC, but with no differences between three groups of clinical severity of illness. For VO₂, similar trends are seen. For
Table 13. Frequency of patterns in progress on six parameters in regular cohort.

| Parameter     | Worse (%) | Stable (%) | Improving (%) | Fluctuating (%) |
|---------------|-----------|------------|----------------|-----------------|
| Breathlessness| 20(24.7)  | 37(45.7)   | 5(6.2)         | 4(5)            |
| FVC, mL       | —         | 8(9.9)     | 23(28.4)       | 21(25.9)        | 29(35.8)        |
| MEFR₂₅₋₇₅, L | 33(40.7)  | 11(13.6)   | 3(3.7)         | 20(24.7)        | 14(17.3)        |
| PEFR, L       | 1(1.2)    | 10(12.4)   | 43(53.1)       | 5(6.2)          | 22(27.2)        |
| O₂ uptake, mL | 4(4.9)    | 5(6.2)     | 32(39.5)       | 16(19.8)        | 24(29.6)*       |
| Hamilton depres-
| score (n=67)  | 15(18.5)   | 12(14.8)   | 10(12.4)       | 8(9.9)          | 22(27.2)        |

Abbreviations: FVC, forced vital capacity; MEFR, maximum expiratory flow rate; PEFR, peak expiratory flow rate.

Table 14. Model building on regular cohort for behavior and multifactorial analysis.

| Factor | Factor 1 | Factor 2 |
|--------|----------|----------|
| FVC    | 0.907    | 0.147    |
| MEFR₂₅₋₇₅ | 0.915 | 0.114    |
| PEFR   | 0.913    | 0.176    |
| Cough  | −0.365   | 0.621    |
| Dyspnea| −0.273   | 0.751    |
| Pco₂   | 0.201    | 0.291    |
| X-ray zones | −0.074 | 0.352    |
| Correlation of severity index | −0.242* | −0.227* |

Eigen value 2.917 1.273
Percent variance explained 52.4

Table 15. Age-sex distribution in relation to clinical severity of initial illness in railway colony patients (1617 cases).

| Clinical illness | Mild | Moderate | Severe | Total |
|------------------|------|----------|--------|-------|
| Age, years       |      |          |        |       |
| 6-39*            | 22+67 | 18+76   | 35+52 | 15+50 |
| 1-19 (%)         | (478) | (58)    | (48.2) | (40.1) |
| 20-44 (%)        | (55.4) | (56.3) | (39.9) | (41) |
| 45+ (%)          | (46.2) | (45.1) | (46.2) | (43.7) |

*Group includes subjects up to 5 years old.
*p < 0.001 for age differences in females.

depression scores, it is seen that in all three groups the scores worsen up to 18 months and then stabilize (slightly lower in mild group only).

As our model was derived on a small cohort based on 0- and 24-month data, data were validated for all six phases; our attempt to project behavior of the railway colony cohort was successful. As there were no significant differences in sequential behavior by age or sex, we applied this further to the affected Bhopal city population.

Table 19 gives the age-sex distribution and clinical severity of illness in the Bhopal city population. This was derived from a full census of the inner city and a random, stratified sample of three variably affected communities. As per design of the Indian Council of Medical Research (ICMR), the cohort was to representative of the general city. Here the age-sex distribution is spread evenly, and distribution of clinical illness grades more equitably. While there are several significant differences between the three populations (our regular, railway colony, and the ICMR cohorts), as the course of MIC-induced disease did not seem to differ by age or sex, we do not think these differences would invalidate application of our predicted model to the general city population.

Table 20 gives projected age-sex standardized (to account for significant differences) sequential behavior of five parameters for the Bhopal city population over 2 years. Thus, for three grades of clinical illness, the behavior does not appear significantly different (therefore listed separately in three groups only for FVC). The patterns of MEFR, PEFR, Vo₂, and depression are also essentially similar to the railway colony cohort. Table 20 also shows some relevant data on abnormal lung symptoms as observed at 3 months and for deaths/1000 at 3 months and 2 years in the three zones of clinically affected grades of city population. It confirms that three zones of differently affected degrees of illness show different morbidity.
Table 18. Projected age-standardized sequential behavior of Bhopal railway colony patients. *

|                | Month | 0   | 3   | 6   | 12  | 18  | 24  |
|----------------|-------|-----|-----|-----|-----|-----|-----|
| FVC, L         |       |     |     |     |     |     |     |
| Mild           |       | 2.02| 2.05| 2.01| 2.66| 2.78| 2.59|
| Moderate       |       | 1.98| 2.01| 1.92| 2.63| 2.76| 2.56|
| Severe         |       | 1.96| 2.01| 1.97| 2.63| 2.78| 2.57|
| MEFR (25-0.75 L/min) |   |     |     |     |     |     |     |
| Mild           |       | 197.5| 214.5| 205.3| 173.7| 163.6| 156.3|
| Moderate       |       | 193.5| 201.3| 203.4| 170.1| 163.4| 154.5|
| Severe         |       | 189.8| 208.4| 201.2| 166.8| 157.2| 152.4|
| PEFR, L/min    |       |     |     |     |     |     |     |
| Mild           |       | 344.4| 376.8| 404.9| 433.8| 458.7| 453.7|
| Moderate       |       | 338.7| 376.4| 402.4| 429.9| 457.8| 451.2|
| Severe         |       | 341.5| 391.5| 406.0| 435.6| 464.3| 457.5|
| VO₂₂, mL       |       |     |     |     |     |     |     |
| Mild           |       | 190.5| 200.8| 204.4| 227.6| 242.8| 228.3|
| Moderate       |       | 189.8| 221.0| 206.1| 228.0| 243.8| 227.2|
| Severe         |       | 182.9| 223.2| 212.3| 229.7| 246.9| 229.8|
| Hamilton depression score |   |     |     |     |     |     |     |
| Mild           |       | 12  | 17  | 15  | 17  | 14  |
| Moderate       |       | 12  | 17  | 15  | 15  | 15  |
| Severe         |       | 11  | 16  | 16  | 15  | 16  |

Abbreviations: FVC, forced vital capacity; MEFR, maximum expiratory flow rate; PEFR, peak expiratory flow rate.

*Values are expressed as means.

Table 19. Age-sex distribution in relation to clinically affected grades in Bhopal city population.

| Age, years | Mild | Moderate | Severe | Total |
|------------|------|----------|--------|-------|
| 0-24       | 5663 | 5141     | 1023* | 8238  |
| (%)        | (22.7)| (23.3)   | (42.2)| (44)  |
| 25-44      | 2691 | 2369     | 4840* | 4164* |
| (%)        | (23.4)| (24.2)   | (42.1)| (42.6)| (34.5)| (33.2)| (5738) |
| 45+        | 1360 | 1178     | 2585* | 2126  | 1793* | 1528  | 5738  |
| (%)        | (23.7)| (24.4)   | (45.1)| (44)  | (31.2)| (31.6)| (4832) |

* p < 0.01.

Table 20. Projected (age-sex) standardized sequential behavior of Bhopal city subjects.

|                  | Month | 0   | 3   | 6   | 12  | 18  | 24  |
|------------------|-------|-----|-----|-----|-----|-----|-----|
| Mean FVC, L      |       |     |     |     |     |     |     |
| Mild             |       | 1.84| 1.92| 1.91| 2.48| 2.57| 2.44|
| Moderate         |       | 1.85| 1.93| 1.92| 2.49| 2.79| 2.45|
| Severe           |       | 1.84| 1.92| 1.92| 2.49| 2.58| 2.45|
| Total            |       | 1.84| 1.92| 1.92| 2.48| 2.65| 2.45|
| Mean MEFR (25-0.75 L/min) |   |     |     |     |     |     |     |
| Mild             |       | 182.2| 200.5| 198.8| 163.6| 174.7| 153.7|
| Moderate         |       | 304.8| 332.6| 382  | 400.2| 439.3| 425.7|
| Severe           |       | 178.4| 214.6| 194.1| 220.1| 240.6| 201.0|
| Depression score |       | 10  | 17  | 13  | 15  | 15  | 14  |

Abbreviations: FVC, forced vital capacity; MEFR, maximum expiratory flow rate; PEFR, peak expiratory flow rate.

We may conclude that the model developed on our cohort of 13 subjects could be applied to the Bhopal city population for judging the sequential behavior of MIC-induced disease.

Discussion

As our findings up to 6 months have already been published (1–3), it is fair to state that our earlier evidence of interstitial restrictive lung pathology with small airway disease is confirmed. The airway component seems to have progressed, leading to a fluctuating course with persisting disability. We found persistent flow rate abnormalities, particularly for V(E75) (E indicates expiratory flow rate; 75 indicates expiratory flow rate 75% of VC). For V/IP (IP, inspiratory peak flow rate), V/(IS50) (I indicates inspiratory flow rate; 50 indicates inspiratory flow rate at 50% of VC), and V/(E75) the improvement was maintained, and for V(EF) (expiratory peak flow rate), V/(E75), and V/(E50) there was a significant decline after 18 months. There were also persistent abnormalities of flow-volume loop (3).

Studies done by Alarie et al. (5) indicate that severe airway obstruction persists after a single MIC exposure (37 ppm for 3 hr) and recovery from pulmonary effects is very slow. Recovery from MIC was considered to be slower than from H₂SO₄, toluene diisocyanate, and wood smoke (5). Alarie et al. claimed that the recovery pattern was similar to that following exposure to smoke from polyvinyl chloride (7). They found VE (expired minute volume) particularly to be reduced, and VT (tidal volume) and respiratory rate did not increase after MIC exposure (5). The type of FV loop abnormalities we reported (3) were similar to those seen by Alarie et al. (5).

Alarie et al. also did not find a cyanidolike effect (5) after 37 ppm of MIC. In view of the controversy of the cyanidolike effects (e.g., a common complaint of persistent muscle weakness) in Bhopal subjects, this may be important. While we have found evidence of rise in COHb and MetHb initially, possibly attributable to effects of breakdown products of MIC, the psychosomatic symptoms of the type discussed earlier seem to be correlated to organic lung disability. As organic lung damage is not known to occur in chronic cyanide poisoning, we think our sequential results also provide evidence against such a theory. Isocyanates have been associated with occupational asthma (8).

Our results show, along with chronic small airway disease, evidence of restrictive lung disease (1,2). These changes may be similar to those observed by Charles et al. (9). What was not known in earlier studies, for MIC-induced disease, was its chronic fluctuating course, for which our follow-up data and model provide evidence.

Schwetz et al. (10) found that 1–3 ppm MIC exposure 6 hr/day for 4 days in mice resulted in a significant number of dead fetuses at birth and a significant decrease in neonatal survival. In the railway colony cohort, there were frequent spontaneous abortions (also in exposed areas of Bhopal), but there was no evidence of increased fetal abnormalities experimentally (10) or in the city population (11).

Other aspects of immunologic, mutagenic, and genotoxic effects due to MIC have been studied by Deo et al. (12). These studies revealed (on a similar group of 67 exposed and 15 control subjects) minor chromosomal aberrations, low responsiveness of lymphocytes to phytohemagglutinin delay in cell cycle, increase in T-lymphocytes, and lowering of sister chromatid ex-
changes. However, such abnormalities were inconsistent and minor; this is confirmed by Tice et al. (13). They found that MIC exposure for 4 days resulted in a small increase in chromosomal aberrations and sister chromatid changes; but no genotoxicity or mutations were found (14). Similar to our findings, specific antibodies have been reported after TDI occupational exposure, which showed a fluctuating, increasing, or declining course (15).

Bucher et al. (16) observed granulomatous inflammation with persistent lung damage, intraluminal airway fibrosis, and bronchiolitis after a 2-hr exposure to MIC in rats (17). Their studies on repeated exposure to 1–6 ppm MIC did not result in significant direct effects on nonrespiratory tissues (18). Our observations conform to this pattern and both corroborate persistent pulmonary damage.

Andersson et al. (19) have presented some data from Bhopal community studies that indicated variations in morbidity according to wind direction. Thus, the railway colony, situated southeast of the factory, suffered a high mortality. Our follow-up data indicates that affected subjects with varying initial severities of illness have a similar course.

Fedde et al. (20) reported low Po2, increased metabolic acidosis, tissue hypoxia, and increased ventilation-perfusion imbalance due to bronchial obstruction after a high exposure (240–628 ppm) of MIC for 15 min. Our findings of early hypoxia and later of small airway obstruction confirm their data; however, within the first few days, there was respiratory alkalosis, but not hypercapnia and acidosis. Several advances have been made in understanding MIC-induced disease since the first article by Kimmmerle and Eben (21). With exposure at 23 ppm MIC, they found heavy breathing, lung edema, and irritation of mucosa (21).

Because of the continued wide use of isocyanates, there may still be large interest in their systemic toxicity. In a study of 783 cases, 2–4 months after exposure to MIC, Rastogi et al. found that females were more seriously affected (22); although major change in lung function was restrictive, obstruction was noticed in some. In another paper from this group on epidemiologic data (23) in a study of 1,209 subjects, most showed respiratory, cardiovascular, abdominal, and skeletal symptoms. Their description of acute cases (24) was similar to other observations (25). Their experimental studies after a single MIC exposure at 3.2 mg/L for 8 min. (26) showed thickening of alveolar septa, lymphoid hyperplasia, peripheral emphysema, peribronchial edema, and cellular infiltrates with exfoliated bronchiolar epithelium. these findings are similar to those of Bucher et al. (16–18).

Our clinical and functional data on follow up amplify in detail some of the lung changes. Our development of a predictive model is unique in an occupational setting, although this has been done by several researchers on experimental or clinical problems. This effort might help in delineating the future course of human effects in relation to such an industrial disaster.

We thank G. B. Parulkar for permitting this study. We sincerely appreciate the continued support of the Indian Council of Medical Research, New Delhi. We also acknowledge technical support of R. K. Agrawal, Chief Medical Officer, Central Railway. Cooperation of several subjects made this follow up at a distance of 500 miles possible.
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