HEALTH EFFECTS OF THE TOXIC GAS LEAK FROM THE UNION CARBIDE METHYL ISOCYANATE PLANT IN BHOPAL

TECHNICAL REPORT ON
Population Based Long Term Clinical Studies
(1985 – 1994)

Bhopal Gas Disaster Research Centre
Gandhi Medical College,
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ACKNOWLEDGEMENTS

The project " Population Based Long Term Clinical Studies on Health Effects of Bhopal Toxic Gas Exposure" has been conducted for almost a decade (1985-1994) and a large number of scientists from different parts of the country have contributed in these studies. Hence, our utmost thanks are due to all these scientists.

Thanks are due to Late Dr.V.Ramalingaswami, Late Dr.A.S.Paintal, Dr.S.P.Tripathi, Dr.G.V.Sathyavati and Dr.N.K. Ganguly, Ex Director Generals, Dr. S.Sriramachari, Dr. Usha K. Luthra, Dr. Padam Singh, Ex. Additional Director Generals, Late Dr. C.R.Ramachandran, Ex.Sr.Deputy Director General, Dr.A.K.Prabhakar, Ex-Deputy Director General, Dr.Rashmi Parhee, Ex-Sr.Research Officer, officers of NCD Division and other members of the Indian Council of Medical Research for technical guidance; and Ministry of Health & Family Welfare for the prompt financial support.

The Council wishes to place on record its sincere thanks to Shri Tanwant Singh Keer, Ex-Minister, Bhopal Gas Relief and Rehabilitation Department, Govt. of Madhya Pradesh, Shri Ishwar Das, Shri S.Satyam and Shri C.S.Chadha, the then Principal Secretaries, Govt. of M.P.Department of Bhopal Gas Relief for enabling such a major activity to be successfully carried out. Dr.P.K.Bhat, the then Director, Centre for Rehabilitation Studies provided valuable support and cooperation in the preparation of this report.

I wish to place on record my sincere thanks to all the team members for their willing cooperation and for their very hard work. Special thanks are due to Dr.S.Sriramachari and Dr.S.K.Jain for facilitating the publication of this Report and to Dr.D.K.Shukla, Scientist-F,NCD,Division, ICMR for assisting them and persiung the progress of this Report. Thanks are also due to the secretarial staff of BGDRC and secretarial staff attached to Dr. S.K.Jain for typing the manuscript of this report. Our sincere gratitude is due to all the people who extended their cooperation and time for participation in this study over a protracted period of time.

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PREFACE

On the night of 2nd/3rd December, 1984, approximately 40 tons of highly toxic Methyl Isocyanate and its reaction products (MIC/Toxic Gas) suddenly escaped in a gaseous form from the Pesticide Plant in Bhopal – owned by the American Multinational Company, Union Carbide Corporation. The Indian Council of Medical Research (ICMR) estimated that out of a total 832904 population of Bhopal, 521262 (62.58%) suffered from inhalational toxicity while 311642 (37.42%) escaped the effect of the toxic gas. It was further estimated that approximately 2000 expose died in the first 72 hours, and a large proportion of the survivors suffered acute multisystem morbidities – eyes and lungs being the main target organs. At this, the Nation was shocked, facing unprecedented health problems of a totally new disease, as nothing was known about its pathogenesis, prognosis and treatment. It was feared that the toxic gas inhalation might lead to progressive multisystem morbidities like chronic incapacitating lung disease; blindness; adverse effects on pregnant women leading to increased incidence of abortions, still births, genetic defects in children to be born; and increased incidence of cancers. This demanded urgent intensive research into population based long term epidemiological studies. Simultaneously, it was necessary to define the clinical spectrum of diseases caused and treat them.

As a first step - based on the mortality data - the ICMR categorized the entire affected population into : severely exposed/affected = 32476 (3.90%); moderately exposed/affected = 71917 (8.63%); mildly exposed/affected = 416869 (50.05%), of the total population.

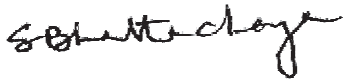
It took a couple of months to register cohorts, prepare study designs and protocols, train field workers, carry out validation tests, before epidemiological data started pouring in. Finally, the population-based long term epidemiological studies from 1985 through 1994 were completed, and the Technical Report later was published by the ICMR. A sense of relief was felt when the results showed continuously diminishing mortality as well as morbidities due to the toxic gas *per se*.

At the same time, clinical research studies were organized to document the natural history of the morbidities caused, and find rational methods of treatment. While state-of-the-art facilities were being created for advanced research, systematic clinical studies were started with the existing facilities, on acute and sub-acute clinical phase, radiological aspects, mental health problems, pulmonary function and arterial blood gases, pregnancy outcome, neurological diseases and immunological, mutagenic and genotoxic aspects. The results of these studies were published in the form of ten papers in the Indian Journal of Medical Research [Vol.86 (Supplement) 1987, pp 1 to 87]. The findings were very useful in guiding further research studies and management of toxic gas related health problems.

As more advanced facilities became available, further long term clinical research studies were planned on all possible aspects of the toxic gas related morbidities. Most of the study samples were taken from the ICMR registered cohorts from the exposed/affected as well as unexposed/control population. Studies also included specially selected samples with specific objectives. It is noteworthy that by the

time these long term studies could take off the ground the inhalational injuries of lung and contact injury of eyes had already started undergoing a process of resolution and recovery. Altogether, more than 60000 study cases from affected population and over 17000 study cases from the control/unexposed population were included in the various research projects, carried out for 4 to 7 years. Most projects were undertaken by the Medical Faculty of Gandhi Medical College but a few were also carried out by scientists from Delhi, Lucknow, Bangalore and Bombay. Besides, a large number of young research officers and para-medical staff and field workers made valuable contribution towards collection of data. It was with the painstaking efforts of all of them that the final project reports could be prepared and submitted to the ICMR, by the respective lead investigators. It is indeed a matter of national pride that at least 90% of the clinical research projects from 1985 through 1994 were accomplished to their logical conclusions. The results were conclusive in that, there were no cases of blindness or any adverse effects on the pregnancy outcomes - attributable to the toxic gas *per se* Furthermore, the acute inhalational lung injury amongst the survivors healed completely or left scars in the lungs, akin to the inhalational injury caused by ammonia, nitrogen dioxide, chlorine etc.

These studies covering all aspects of different morbidities are being presented in the Technical Report on Clinical Studies in the form of fourteen chapters. It is a matter of great relief that the results showed downward trends in morbidities. By and large, the results were found to be in consonance with the results of the epidemiological studies published earlier.



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CONTENTS

ABBREVIATIONS/EXPLANATIONS

ABG	arterial blood gases
ARDS	acute respiratory distress syndrome
BAL	bronchoalveolar lavage
Control Area	areas of Bhopal not affected by MIC/Toxic Gas
COPD	chronic obstructive pulmonary disease
CPET	cardio-pulmonary exercise test
DLCO	carbon monoxide diffusing capacity of lungs (single breath)
$FEF_{25,50,75}$	forced expiratory flow rates at 25, 50, 75 percent of forced expiratory vital capacity respectively
FEF/FMF_{25-75}	forced mid-expiratory flow rate
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
FVC	forced vital capacity
HBCR	Hospital Based Cancer Registry
HCN	hydrocyanic acid
HCO_3	bicarbonate level in plasma
ICMR	Indian Council of Medical Research
KCO	diffusing capacity of lungs per unit lung volume
MIC	Methyl Isocyanate
Mild Area	areas of Bhopal mildly affected by MIC/Toxic Gas
Moderate Area	areas of Bhopal moderately affected by MIC/Toxic Gas
MVV	maximum voluntary ventilation
NaTS	sodium thiosulphate
NCRP	National Cancer Registry Programme
PAC	Project Advisory Committee
PBCR	Population Based Cancer Registry
PEFR	peak expiratory flow rate
PFT	pulmonary function test
$PaCO_2$	arterial blood carbon dioxide tension (mmHg)
PaO_2	arterial blood oxygen tension (mmHg)
pHa	pH of arterial blood
$PVCO_2$	mixed venous blood carbon dioxide tension (mmHg)
RADS	reactive airway dysfunction syndrome
RQ	respiratory quotient
RV	residual volume
Severe Area	areas of Bhopal severely affected by MIC/Toxic Gas
SVC	slow vital capacity
TLC	total lung capacity
Toxic Gas	methyl isocyanate and its reaction products
VA	alveolar volume during DLCO measurement
VE	minute ventilation
$VE\ Max_{50,\ 75}$	maximum expiratory flow rate at 50% and 75% of forced expiratory vital capacity
VO_2 max	maximum oxygen uptake during exercise

INTRODUCTION

CLINICAL STUDIES ON THE METHYL ISOCYANATE (MIC) TOXIC GAS EXPOSED POPULATION OF BHOPAL

Toxic Gas Leak and Its Aftermath

Sudden leakage of tons of Methyl Isocyanate (MIC) from a storage tank at the Union Carbide Factory in Bhopal on the night of 2nd-3rd December, 1984, had caused death of more than 2,000 people over the following 3 days, from amongst an estimated population of over 5 lacs (out of a total of 8 lacs) who were actually exposed to the toxic MIC and its reaction products together called toxic gas. The circumstances under which the toxic gas leaked from the Union Carbide Factory, and what followed are described in the first ICMR Technical Report : Population Based Long Term Epidemiological Studies (1985-1994)[1]. Based on the prevailing meteorological conditions it was observed that strong inversion currents prevailed at that time of the night slowly drifted the toxic cloud, affecting both human and plant life along its path over an area of approximately 40 sq km. Since it was a comparatively cold and humid night the toxic gas cloud behaved like an 'aerosol', settling on the adjoining area in the shape of a mushroom, engulfing the population and then gradually spreading to the neighbouring areas. A large proportion of the exposed population inhaled this 'aerosol' and instantly developed acute respiratory symptoms; also contact with eyes produced acute severe eye problems. In utter panic, they ran helter skelter, seeking protection and relief.

The medical professionals at Bhopal faced a situation in the early hours of December 2-3, 1984 which was unparalleled in the annals of medical history. Thousands of very sick people thronged the corridors of the hospitals; gasping for breath, frothing at mouth, congested watery eyes unable to see clearly, retching and vomiting, with fear and panic writ large on their face. A team of local doctors including the Gandhi Medical College staff, para-medical and social workers under the able and dynamic leadership of Dr.N.P.Misra promptly moved into action to organize medical relief to the lacs of suffering people, thus saving thousands of lives. They also looked at the totality of the problems created by the disaster so that immediate and long term medical relief measures could be organised.

A quick estimate suggested that approximately 100,000 persons residing in areas close to the Union Carbide Factory would have been exposed to relatively higher concentration of the potentially lethal toxic gas than the areas farther away. Inhalational deaths occurred instantly at home, in streets and in hospitals. Besides the dead, lacs of the exposees constituting about 60% of the total 8 lac population of Bhopal suffered from respiratory, ophthalmic, musculoskeletal, neuropsychiatric and gastrointestinal symptoms.

While the healthcare providers with severely constrained infrastructure grappled with the gigantic task of providing medical relief to save lives, the scientists across the country who had immediately realized the gravity and complexity of the situation were deeply concerned with the following long term aspects of the disaster:

1. The observed mortality and morbidity pattern clearly indicated that the toxic gas was potentially lethal and may cause many more deaths and diseases in the near and distant future.
2. It was most disturbing that nothing was known about the exact composition of the toxic gas or its antidotes.
3. MIC being a highly reactive chemical may adversely affect the pregnancy outcome, causing abortions, still births or congenital anomalies. There was also the possibility of the incidence of cancers going up.

4. A large number of exposees may suffer from chronic, progressive multi system morbidities and disabilities for a long time or entire life, it was feared!
5. It was necessary to conduct clinical and epidemiological research studies to understand the etiopathogenesis and natural history of the morbidities caused so that rational methods of therapy and prevention of serious disabilities could be evolved.
6. There was an urgent need to strengthen, upgrade or create new medical and epidemiological research facilities in Bhopal.

The Indian Council of Medical Research (ICMR) set up more than 20 research projects on the epidemiological and clinical aspects of the diseases caused by the inhalation of the toxic gas. Also, scientists from other parts of the country offered their research expertise to undertake planned studies on the epidemiological, clinical and toxicological aspects of the resultant morbidities. To quote a few instances:

1. Prof.A.S.Paintal, Director, Vallabhbhai Patel Chest Institute, University of Delhi and Head, DST Centre for Visceral Mechanisms, set up a state-of-the-art Pulmonary Function and Exercise Test laboratory at the Gandhi Medical College in Bhopal and deputed Prof.S.K.Jain, Head, Department of Cardiorespiratory Physiology and Clinical Unit III, V.P.Chest Institute, to undertake research studies on respiratory problems.
2. Dr.S.R.Kamat and his co-workers at the KEM Hospital, Bombay took acutely ill patients to Bombay for investigation and management.
3. Dr.P.S.Narayanan, Head, Cardiac Surgery Department, G.B.Pant Hospital, New Delhi set up a Centre for investigation in Bhopal.
4. Dr.V.K.Vijayan of Tuberculosis Research Centre, Madras set up laboratory in Bhopal to do endoscopies and study bronchoalveolar lavage (BAL) in the affected population which would throw some light on the evolution of toxic gas caused lung morbidities.

It cannot be over-emphasized that the main research base was provided by the Dean and Medical Faculty of the Gandhi Medical College, headed by Dr.N.P.Misra. They were responsible for planning, conducting, supervising, most of the research projects, besides providing facilities for others to carry out their own research studies. Thus, in the years to follow, a large number of research projects were accomplished and their final reports submitted to ICMR by their respective Principal Investigators. The present technical report on Clinical Studies has been compiled on the basis of these final reports, with the necessary editing of course. The Report on Clinical Studies on Methyl Isocyanate (MIC)/Toxic Gas Exposed Population of Bhopal is presented in the form of 14 Chapters (see contents). A synopsis of all clinical studies is also presented.

Reference

1. ICMR Technical Report. Health Effects of the Toxic Gas Leak from the Union Carbide Methyl Isocyanate Plant in Bhopal : Population Based Long Term Epidemiological Studies (1985-1994).

S.K.Jain

Synopsis of Clinical Studies in Methyl Isocyanate (MIC)/Toxic Gas Exposed Population of Bhopal

CHAPTERS 1 TO 14

(For details, see the respective chapters)

Chapter 1

Early phase observations including clinical, radiological and pulmonary function studies in MIC/toxic gas exposed population in the acute and subacute phases

Objectives

To document clinical manifestations in the acute and subacute phases of respiratory disease caused by inhalation of MIC/toxic gas.

ACUTE PHASE (PERIOD: SOON AFTER GAS EXPOSURE)

Study Sample

978 patients with acute severe illness admitted to Hamidia Hospital soon after the gas episode were investigated and treated. Data of 544 patients were analysed.

Clinical Symptoms, Physical Signs and Chest Radiography

Clinical Symptoms

Respiratory. Breathlessness (98.9%); cough (98.4%), pink froth at mouth (52%), irritation in throat with choking feeling (46%), pain chest (25%), expectoration (16%), haemoptysis (12.6%), hoarseness (2%).

Ocular. 85.8% patients had irritation, lacrymation, photophobia, blurred vision, foreign body sensation in the eyes.

Gastro-intestinal. Loss of appetite (91.7%), nausea, retching and vomiting (52%), epigastric discomfort (18.9%).

Neuro-psychiatric. Extreme myasthenia-like weakness (25%), apathy and listlessness (21.9%), hypersomnolence (16%), coma (7.2%), tremors (2%), tetany (0.9%), neurotic depression, anxiety state, adjustment reaction (19.6%).

Physical Signs

Tachycardia (54%), bradycardia (1.2%), respiratory rate per min: <20 (12.1%), 20-40 (59.5%), >40 (20.2%), gasping (7.1%), fever (2.4%), rhonchi and crepts (83.1%) and pleural rub (1.2%) on auscultation of chest.

Chest Radiography

Diffuse, mostly bilateral non-homogeneous ground glass, punctate, linear, micronodular opacities (98%). By the end of 2 weeks there was marked cleareance in most cases.

SUBACUTE PHASE (PERIOD: JANUARY – MARCH, 1985)

Study Sample

Data of 129 persistently symptomatic patients seen at MIC Clinic of Hamidia Hospital were analysed. Males (90) – age: 34±11.5, height: 1.67±0.07M, weight: 52.1±12 kg. Females (39) – age: 30.9±10.3, height: 1.54±0.005M, weight: 46±12.2 kg. Severity of exposure was: severe (51.2%), moderate (38%), and mild (10.8%).

Symptoms and Signs

The most prominent symptoms were: exertional breathlessness (90%), cough (74%), and chest pain (33%). 61.2% of 129 patients had no physical signs in chest, others had rhonchi and or rales. These were not related to infection but were attributed to the toxic gas inhalation *per se*.

Chest Radiography

The PA chest radiographs were read as: normal (44.2%), prominent bronchovascular markings (43.4%), reticular opacities (17.1%), pleural pathology (2.3%), raised diaphragm (1.6%) and cardiomegaly (0.8%).

Pulmonary Function Studies

Spirometry test was done with portable Vitalograph. The results of forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and forced mid-expiratory flow rates (FMF_{25-75}) were expressed as percentages of predicted normals. The cut-off points 75% for FVC and 75% for FEV_1/FVC were used to classify the test findings as: normal, obstructive, restrictive, obstructive cum restrictive (combined). Since the smokers and non-smokes did not show any significant difference, the data of the two groups were pooled for analysis. All test values were expressed as percent of predicted. The mean test values were found to be: FVC = 85.6±21.0% in males and 82.0±24% in females; FEV_1 = 84.1±28% in males and 83.4±29.5% in females; FMF_{25-75} = 82.8±43.4% in males and 74.2±40.9% in females. The mean FEV_1/FVC% were found to be 77.1±11.8 in males and 80.2±11.8 in females. Further analysis of spirometry data showed that out of the 129 cases, 55.8% had normal test values, 10.1% revealed airflow obstructive disorder, 12.4% had restrictive pulmonary impairment, while 21.7% had obstructive-cum-restrictive (combined) pattern. Thirteen of the 31 patients tested had shown significant broncho-reversibility after inhaled bronchodilator aerosol, suggesting the possibility of "reactive airway dysfunction syndrome". It is noteworthy that there was no consistent relationship between clinical signs and symptoms, chest radiography and impaired lung function.

Lung histo-pathology in three cases of open lung biopsy revealed pleural fibrosis with focal mesothelial proliferation, thickened inter-alveolar septa, mono-nuclear cell infiltration in bronchial and peribronchial tissues, patchy peribronchial and perivascular fibrosis, destruction of bronchial wall and epithelium. In one case typical lesion of bronchiolitis obliterans was seen.

Conclusions

1. In the acute phase of toxic gas exposure, 99% of severely exposed patients suffered from breathlessness, cough, ocular symptoms and abnormal chest radiographs. They improved with time.
2. Lung histopathology in 3 open lung biopsies after 3-4 months showed alveolar, bronchial and peribronchial lesions in the form of inflammation, destruction and fibrosis.
3. In the subacute phase, impairment of lung function could also be demonstrated.
4. Number of Tables = 1.1 to 1.8.

Chapter 2

Pathophysiology of lung disease caused by inhalation of MIC/toxic gas: based on serial studies of pulmonary function, arterial blood gases, acid-base and cardio-pulmonary exercise test

Objectives

To define structure-function relationship in lung disease caused by MIC/toxic gas inhalation, based on long term follow-up studies. Also, to evaluate mechanisms underlying the clinically unexplained dyspnoea, and inability to work.

Study Period (April 1985 to March 1990)

The first case was studied 128 days after the gas exposure while the last follow-up case was studied 1896 days following the gas exposure. The initial study (S1) was followed by 1st follow-up (S2) 6–12 months after S1; 2nd follow-up (S3) 4–5 years after S1.

Study Sample

After a door to door survey of the severely exposed/affected areas and from the MIC ward of Hamidia Hospital, one hundred nineteen very severely affected patients were identified for investigation. The inclusion was based on high severity score determined by history of exposure, severe persistent symptoms, chest radiograph changes, hospitalisation, death in the family or immediate neighbourhood, history of disturbed consciousness etc.

Physio-Clinical Characteristics

There were three subgroups: 1. Non Smoker Males (NSM) – 54: mean age = 34±14.2, BMI = 19.6±4.4, Hb = 13.1±1.4; 2. Smoker Males (SM) – 24: mean age = 39±10.8, BMI = 18.5±3.6, Hb = 13.3±1.2; 3. Females – 41: mean age = 32±12, BMI = 20.2±4.6, Hb = 11.6±1.5. Nearly 50% of the subjects were assessed to be malnourished on the basis of BMI values.

Clinical Profile

All patients at the time of initial study S1 were symptomatic with reduced capacity to work (100%) because of dyspnoea on exertion (96%), cough (80%), pain chest (66%). Only 46% showed +ve signs in chest on auscultation. Chest radiographs of 80% of them showed abnormalities like linear, reticulo-nodular opacities, honey-combing and hyperinflation etc.

Pulmonary Function, Arterial Blood Gases and Cardio-pulmonary Exercise Test (CPET) Studies

The physical characteristics and pulmonary function test values of non smoker males did not differ significantly from smokers. Thus, they were mostly presented as one group.

PULMONARY FUNCTION TESTS

Static lung volumes. In males, the mean slow vital capacity (SVC) was reduced to nearly 78% of normal, while mean residual volume (RV) was increased to 118% of normal. These changes were statistically significant and also physiologically abnormal. Increased RV meant that the terminal airways closed prematurely during expiration, thus trapping part of the SVC in the alveoli – an indication of narrowed peripheral/small airways. It was noted that the median changes in SVC and RV could be accounted for by the abnormal values in 60% of the patients. Mean functional residual capacity (FRC) value was close to normal, indicating no shift in the mid-thoracic position. Mean total lung capacity (TLC) – the sum total of SVC and RV – showed a marginal reduction which was not statistically significant. Nonetheless, this was believed to be due to alveolo-pleural involvement. Six percent of the cases showed ≥120% TLC indicating hyperinflation due to emphysema or excessive alveolar air trapping. Further analysis of data showed that 80% of the patients had normal TLC, while 20% had mild to moderate reduction. Compared with males, the female patients showed a relatively greater reduction of SVC, a lesser increase of RV, and a significant reduction of FRC and TLC. Thus, there was marginal reduction of lung size. This was noted to be the result of moderate or severe reduction of TLC in 32% of the patients, being normal in the remaining 68%. The RV/TLC ratio was normal in 48% of male and female patients, 25.4% showed mild and 26.3% showed moderate or severe increase of RV/TLC%, again reflecting on increased residual volume due to alveolar air trapping.

Dynamic lung volumes. The forced vital capacity (FVC) in males and females followed the same pattern as the SVC. It is well known that forced expiratory volume in first second (FEV_1) is a very important measurement which correlates well with arterial blood gases, exercise capacity and is the gold standard for diagnosis of airflow obstructive disorders like asthma and COPD. The mean FEV_1 values both in males and females showed a mild but statistically significant reduction. Further analysis of data showed that 33% patients had normal FEV_1, 33% showed mild reduction, 21% showed moderate reduction while 13% showed severe reduction. Ratio of FEV_1/FVC% was found to be normal in 87% cases, and reduced in 13% cases. Based on 75% as the cut-off point for FVC and FEV_1 between

normal and abnormal, it was found that 42.9% cases were normal, 22.2% showed restrictive, 11.8% obstructive and 25.2% restrictive cum obstructive (combined) pulmonary impairment in both male and female patients.

Expiratory flow rates. Forced expiratory flow rates (FEF) are a reliable and sensitive measure of airflow obstruction. Of these, peak expiratory flow rates (PEFR) and FEF_{75} measurements are considered to be more effort dependent than FEF_{25-75} and FEF_{50}. Mean values of FEF_{50}, FEF_{25-75} and FEF_{75} in males and females in 60 to 90% cases were less than 80% of predicted. The FEF_{75} values were the worst affected, being normal in 10% and impaired in 90% cases: 15% mild, 22% moderate and 53% severe. This showed that small/peripheral airways less than 2.0 mm dia. were worst affected. It also explained the reduction of vital capacity, increased RV and alveolar air trapping and therefore causing only marginal reduction of TLC.

Maximum voluntary ventilation (MVV). The MVV in all study groups showed mild reduction in 35-50% patients, being normal in others.

Broncho-reversibility. The response of FEV_1 to inhalation of 400 μg salbutamol was used to test the degree of broncho-reversibility. An increase of more than 15% with at least 200 ml increase in absolute value of FEV_1 was considered as evidence of asthma. The latter kind of response was seen in 6 of the 94 patients tested. As these patients had resolutely denied any pre gas-exposure history of asthma, it is possible that they had developed asthmatic response as a sequela to toxic gas inhalation.

Single breath CO diffusing capacity (DLCO) of lungs. Out of the 109 patients tested for DLCO, 70% showed normal values, 30% showed statistically significant reduction: 29% mild, 1% moderate while none showed severe reduction. These findings could be explained on the basis of mild reduction of TLC which reduced the surface area available for gas exchange. In no way, this was suggestive of diffuse alveolitis/ interstitial lung disease. Thus, the integrity of alveolar-capillary area largely remained intact, without the gross involvement of gas exchanging units by fibrosis. Mean KCO values, i.e. DLCO divided by TLC(L) were higher than normal. This may be because of reduction of total lung capacity with normal DLCO.

ARTERIAL BLOOD GASES

Arterial blood gases, pH and HCO_3. These measurements actually showed the efficiency of integrated function of ventilation, blood flow in lungs (perfusion) and the process of gas exchange between blood and alveolar air. Arterial blood was examined in 96 out of a total of 119 patients. Mean values of PO_2, PCO_2, pH and HCO_3 were found to be largely within the normal range. Only 6% of the cases showed marginal reduction of PO_2, but they were not in respiratory failure.

Follow-up studies S2 and S3 – compared with S1. The first follow-up study i.e. S2 (59 males, 25 females) was conducted about 6-12 months after the initial study, i.e. S1. The second follow-up study, i.e. S3 (34 males, 12 females) was conducted 4-5 years after S1. The pulmonary function, CO diffusing capacity of lungs and arterial blood gases, pH values of S2 and S3 respectively were tabulated as difference from the S1 values. Statistical analysis of data showed that in the first follow-up, most parameters showed a trend towards improvement which was somewhat reverted back in the S3. It should be understood that there would be some natural loss of lung volumes due to ageing in 4-5 years especially when at least 80-85% cases showed persistent impairment of lung function after the acute lesions had healed naturally or with treatment. Further analysis of data showed that the test values of S2 and S3 varied on both sides of the S1 values, indicating that this was apparently due to variations in the clinical condition of patients with partially damaged lungs leaving scars in the airways and alveoli. The latter may predispose them to the deleterious effects of infections and environmental pollution.

CARDIO-PULMONARY EXERCISE TEST

CPET was performed in male patients to test "aerobic work capacity" and to evaluate mechanisms underlying exercise limitation, unexplained exertional dyspnoea and pulmonary disability – whether it is cardiac, respiratory, metabolic or psychogenic. Maximum symptom limited incremental work load (ramp pattern) bicycle ergometry test was performed in 53 males (36 smokers and 17 non smokers). The basic characteristics and the results of study in smokers and non-smokers did not show any statistically significant difference. It was found that only in 38% patients exercise was limited by severe

breathlessness, the other more common causes being mild and moderate breathlessness, discomfort in calf muscles, knee joints and feet; most patients complained of more than one symptom. The oxygen uptake at break-point of exercise was far below the predicted. More importantly, at the break-point, the patients were still left with plenty of breathing and cardiovascular reserve. The Veq., RQ and oxygen pulse values suggested normal metabolic function at the tissue level. The FEV_1 was normal in 37.7%, mildly reduced in 30.2%, moderately reduced in 22.6% and severely reduced in 9.4% of the patients. It was concluded that the exercise capacity of patients was reduced, producing dyspnoea and disability due to combination of reduced FEV_1, psychogenic factors including poor effort, physiological deconditioning, high level of anxiety, and protein malnutrition. The follow-up CPET in 27 patients showed responses similar to the initial study.

Conclusions

A single one-time inhalation of MIC/toxic gas in a group of 119 severely exposed patients produced acute inflammation of airways and alveoli. The healing of acute lung injury resulted in alveolo-pleural fibrosis and airway constricting lesions, much more in the peripheral/small airways less than 2 mm internal dia. than the central airways. These constrictive bronchiolitis/bronchiolitis obliterans lesions were like those seen in inhalational injury due to ammonia, nitrogen dioxide, ozone etc. The alveolar lesions healed like cryptogenic organizing pneumonia (boop). There was only mild involvement of alveolocapillary membrane in a small proportion of cases. The arterial blood gases were disturbed only in a small proportion of cases. Pulmonary disability was caused by reduced FEV_1, psychogenic factors, physiological deconditioning and malnutrition. In the future, such patients with evidence of residual lung damage might run a clinical course similar to COPD, with recurrent respiratory illnesses.

Number of Tables = 2.1 to 2.26

Chapter 3

Radiological manifestations in the skiagrm of chest and follow-up study of the MIC/toxic gas affected population

Objectives

To document chest radiographic changes in toxic gas affected population and correlate the same with pulmonary disability.

Clinical Study Samples and Periods of Study

Group a consisted of ive hundred patients (263 males, 237 females) with severe respiratory symptoms who reported at the Gandhi Medical College (GMC) Hospital immediately after the toxic gas inhalation.

Group b consisted of a total of 9569 patients, studied from the date of exposure to September 30, 1986, of whom 5247 cases were from out-patients and 4322 cases from the MIC wards of Gandhi Medical College.

Group c consisted of cases from the ICMR registered cohorts in 3 phases. Phase I (period: February 1, 1985 to April, 1988) included a total of 2709 subjects from the exposed areas and 1774 from the unexposed/control areas. Phase II (period: May, 1988 to April, 1989) included 470 “coded cases” from exposed areas and 105 from control areas for in-depth study drawn from 2500 cases who were being followed up. Phase III (period: May, 1989 to April, 1990) covered 175 cases from in-depth Phase II study who were further followed up.

Radiological Observations

The chest radiographs were read by a panel of experts – three physicians and one radiologist. In a representative sample, modified ILO (1980) guidelines were used in the classification of the x-ray opacities. The following are the salient observations in the different Groups and Phases, where applicable.

Group a. All the 500 acute phase chest radiographs were analysed. Only 2.2% were found to be normal, 7.2% were suspected to have pre-existing lung disease as well. A majority of all the rest

showed bilateral interstitial and alveolar oedema, and pneumonitis. Gradually, the x-ray changes cleared leaving residual streaky, nodular, reticulonodular, punctate, fibrotic opacities.

Group b. Of the 9569 patients in this group, 55.4% had normal chest radiograph, 20.5% showed interstitial reaction, 2.1% showed interstitial/alveolar oedema; 8.3% had shadows consistent with pneumonitis, collapse, consolidation, pleural effusion, pneumothorax, pneumo-mediastinum; and 13.7% were suspected to have pre-existing lung disease. Of the 672 radiographs analysed according to modified ILO (1980) guidelines, 511 (76.4%) were found to be normal (0/0); 161 (23.6%) showed abnormalities ranging from 1/1 to 3/3. Of the 100 control cases taken for comparison, 88% were found to be normal (0/0) while the remaining 12% had abnormalities ranging from 1/1 to 3/2.

Group c. Phase I. Findings in 2709 subjects from affected areas were compared with those in 1774 subjects from "control areas". 6.1% of the chest radiographs from affected areas showed suspected tuberculosis and 10% showed interstitial reaction; the corresponding figures for the control areas were 2.9% and 5.1%, respectively.

Findings including pulmonary disabilities and abnormal pulmonary function tests (PFT). The main abnormality in chest radiographs was interstitial reaction. Out of the total number of affected population showing interstitial reaction, 89.9% had pulmonary disability, and 72.5% had abnormal PFT. The corresponding figures in the "control population" were 18.9%, pulmonary disabilities and 43.2%, abnormal PFT findings. Detailed analysis according to severity of exposure showed that in severely exposed 92.6% had pulmonary disabilities and 72%, abnormal PFT; in moderately exposed group, the corresponding figures were 92.4% and 78.3%, and in the mild exposed group, these were 73.3% and 53.4% respectively.

Phase II – in-depth study. In the affected group, 444 cases and in the control group 105 cases were analysed and details of the comparative findings are as follows. "Affected vs Controls": normal – 46.4% *vs* 71.4%; perihilar, peribronchial fibrosis consistent with chronic bronchitis – 22.1% *vs* 12.4%; destructive lesions like TB – 2.9% *vs* 5.7%; and cardiac abnormality – 2.7% *vs* 1.9%.

Phase III. 175 cases from in-depth study of Phase II were further followed up in Phase III. 55.4% cases were normal, 44.6% were abnormal. In the latter group males were affected more than females. The main abnormality was again interstitial reaction (33.1%) and pulmonary tuberculosis (6.4%), while 60.5% were normal.

Conclusions

Acute exposure to MIC/toxic gas resulted in alveolar and interstitial pulmonary oedema, inflammatory, bronchial and peribronchial lesions in chest radiographs – the extent of lesions apparently was determined by the severity of exposure.

Following the exposure the chest radiographs started showing evidence of clearance. However, in the chronic phase, a proportion of cases were left with residual lesions, consisting of alveolar, interstitial, peribronchial inflammation, destruction, fibrosis and airway narrowing.

Number of Tables = 3.1 to 3.8

Chapter 4

Broncho-Alveolar Lavage (Bal) Studies in MIC/Toxic Gas Affected People At Bhopal

ObjectivesTo study inflammatory and immune effector cells in the lower respiratory tract of MIC/toxic gas exposed population to explore the possibility of the existence of alveolitis. If so, is there any evidence of elevated levels of mediators such as fibronectin in BAL fluid ?

Study Sample and Study Period

Broncho-alveolar lavage (BAL) was done in 56 toxic gas exposed patients (51 males, 5 females) with persistent respiratory symptoms, who had 'willed' for the procedure, with the clear objective of finding evidence of inflammatory and immune effector cells and their mediators in the lower respiratory tract. The study was repeated a second time in 20 patients, a third time in 4 patients, and 4th time in one

patient. The results were compared with 17 non-smoking normal individuals from Madras. The study period was 1 to 6 years after the gas exposure.

Severity of Exposure
The severity of exposure was assessed to be mild (6), moderate (10), and severe (40).

Observations and Conclusions

1. Macrophage-neutrophilic alveolitis was present in a proportion of severely exposed patients evaluated 1- 6 years after the exposure.
2. The higher total cells in severely exposed smokers compared to non-smokers suggested that smoking was a risk factor.
3. Repeat lavage studies demonstrated that macrophage alveolitis observed 1-3 years after the exposure progressed to macrophage-neutrophilic alveolitis with time.
4. Fibronectin (one of the toxic mediators released by activated macrophages) levels were elevated in a proportion of patients which persisted in some of them on repeat studies.
5. The exaggerated number of alveolar macrophages and neutrophils in the lower respiratory tract along with elevated levels of fibronectin would suggest that alveolitis in them might have caused further injury and fibrosis of lung parenchyma.
6. The finding of significant negative correlation of neutrophils with FEV_1 and $FEV_1/FVC\%$ further suggested that cells causing alveolitis especially neutrophils could have deleterious effect on lung function..

Number of Tables = 4.1 to 4.5

Chapter 5
Respiratory epidemiology of mic / toxic gas affected population

Objectives
To study the pattern and course of pulmonary disease in the toxic gas exposed population.

I Field study
II In-depth study

I FIELD STUDY

Study Period: Mid October 1985 to April 1988

Study Sample
Random sample of 7010 affected/exposed population and 2500 control/unexposed population were selected for the study, actually covering 4938 (70%), and 1936 (77%) respectively. The age range was 0 to >60. Males constituted 47.5% of the affected and 40.9% of the controls; the corresponding figures for females were 52.5% and 59.1% respectively. The affected group comprised 42.1% from severely exposed area, 46.7% from moderately exposed and 11.3% from mild exposed area.

Symptoms and Signs
98% of the affected group and 19% of the control group suffered from cough, 92% of the affected group and 10% of the control group suffered from dyspnoea – the two symptoms did not correlate with severity of exposure. Incidence of muscular weakness, wheezing and disturbed consciousness were directly related to severity of exposure. Naso-bronchial allergy was significantly more common in the affected than controls, but varied inversely with the severity of exposure. Only 8-10% of the exposed group and 2-4% of the control group had rales and rhonchi on auscultation of chest.

Hospitalisation
Hospitalisation sometimes repeated for respiratory problems was required in 30% of severely exposed, 15.5% of moderately exposed and 4.5% of mild exposed subjects. Clinical evidence of hypoxaemia

requiring oxygen therapy was present in 7.8% severely exposed, 2.9% moderately exposed and 1.4% mildly exposed, compared with controls (0.1%).

Chest Radiograph

Chest radiographs were available for examination in 1550 (31.4%) exposed and 835 (36.4%) control subjects. Of the available chest radiographs, 71% of the exposed and 84% of control subjects were normal. The exposed group showed interstitial lesions in 218 (14%), peribronchial fibrosis (5%), pulmonary tuberculosis in 100 (6%); the corresponding figures in the control group were: 58 (7%), 8 (0.1%) and 17 (2%) respectively.

Pulmonary Function Studies

Pulmonary function was tested with a portable unit – "Spirocheck". Mean FVC and FEV1 were significantly lower in the exposed group than the control group. The cut-off point between normal and impaired function was 80% of predicted. The assessment was rated as: normal = 36% exposed and 82% controls; restrictive ventilatory defect: 50% exposed and 12% controls; airway obstructive: 7% exposed and 4% controls; obstructive cum restrictive: 7% exposed and 2% controls. The pulmonary function abnormalities were more frequent and more intense in severely and moderately exposed than the mildly exposed. The abnormalities in mildly exposed were more than in the "control group". No systematic or consistent relationship was found between pulmonary function test data and chest radiographic findings.

Clinical Diagnosis

In the exposed/affected vs control population, the following clinical diagnoses were suggested: chronic bronchitis ─ 17% *vs* 7%; bronchial asthma ─ 12% *vs* 5% classified as "reactive airway dysfunction syndrome" (RADS); unspecified lung disease ─ 57% *vs* 0.2%; pulmonary tuberculosis ─ 2% *vs* 1%.

IN-DEPTH STUDY

Study Period: starting from May 1988 to April 1989 and 1989-90

Study Sample

From the field study cases, a sample of 311 subjects was selected for "in-depth study". On the basis of respiratory symptomatology, chest radiograph and pulmonary function test results these were divided into five Groups. Fifty healthy subjects were also included to act as "controls" for comparison.

Investigations

Investigations included detailed clinical evaluation, pulmonary function studies (PFT) using Morgan Transfer Test Model C, yearly chest radiograph and broncho-reversibility test. Small airway obstruction was diagnosed on the basis of normal FVC and FEV_1, and when at least 3 of the following 5 were present: VEmax 50% and 75% less than 75% predicted, FEF_{25-75} less than 75% predicted, RV/TLC% more than 45% and difference in VA and TLC more than 500 ml.

Subjective and Objective Scoring System

Based on subjective symptoms and objective parameters as yearly decline of FEV1, chest radiography ─ the course of disease was assessed as "improvement, deterioration, stationary or fluctuating".

Results

Of the 311 subjects, data in 288 were available for analysis, 175 belonged to severely exposed, 113 to moderately exposed category, 147 were males and 141 were females, 41% males were smokers.

Chronic Bronchitis

70 (24%) were classifed as chronic bronchitis – 44 from severely exposed and 26 from moderately exposed categories. Thirty-three patients had persistent airflow obstruction while the remaining 37 did not. Of these 37, seven showed decline of FEV_1 of ≥70 ml (normal <40 ml) in one year.

Reactive Airways Dysfunction Syndrome (RADS)
Seventy patients showed episodic airflow obstruction as in asthma. Six of them had previous history of asthma while the remaining 64 patients were clinically diagnosed as RADS.

Small Airway Disease
Patients who were earlier diagnosed as restrictive pulmonary disease on the basis of FVC and FEV_1 alone, when tested for expiratory flow rates and lung volumes, were actually found to suffer from small airway disease. They had reduced values of VE max 50%, 75% and FEF_{25-75}. Thus, 13.2% of in-depth study patients were diagnosed as small/peripheral airway disease.

Restrictive Pulmonary Impairment
Four patients from the severely affected group were diagnosed to have restrictive pulmonary impairment on the basis of reduced total lung capacity (TLC) to <75% predicted. Two of them also had cough and exertional dyspnoea and reticular/reticulonodular opacities in chest radiographs.

Pulmonary tuberculosis was diagnosed in 24 (8.3%) of exposed group compared with 6% controls. Emphysema with increased total lung capacity and lung hyperinflation was found in three and bronchiectasis in two patients.

Clinical Course
Thirty-two (11%) patients improved, 46 (16%) showed overall deterioration, 76 (27%) showed fluctuating course, and 110 (38%) were stationary. Deterioration was more common in severely affected than in moderately exposed subjects.

Conclusions
Study of a large sample of toxic gas exposed subjects compared with unexposed subjects suggested the following clinical diagnoses: Exposed vs Controls: chronic bronchitis ─ 17% vs 7%; bronchial asthma ─ 12% vs 5% classified as "reactive airway dysfunction syndrome (RADS)"; unspecified lung disease including small airway disease ─ 57% vs 0.2%; pulmonary tuberculosis ─ 2% vs 1%.

Number of Tables = 5.1 to 5.21

Chapter 6
Long term follow-up study especially of pulmonary function in MIC/toxic gas exposed patients

Objectives
Long term, yearly follow-up of clinical profile, radiological and pulmonary function studies in toxic gas exposed population.

Study Sample (Study Period: December 1984 – December 1989)
250 patients (67.2% males, 32.8% females), out of whom 141 (56%) were severely affected, 69 (28%) were moderately affected, 40 (16%) were mildly affected in 1984. On last follow-up in 1989, only 168 were available (males 67%, females 33%): exposure-wise, severe 107 (63.6%), moderate 35 (21%) and mild 26 (15.4%). Controls: 100 age, sex matched subjects from the ICMR designated control area were studied for comparison.

Clinical Profile
Exertional dyspnoea was the commonest symptom (98%) initially and during follow-up. Chest pain, inability to work, cough and expectoration improved over the initial one year followed by a stationary pattern in majority (70%) of cases. Mean frequency of chest infections decreased, although incidence of recurrent respiratory infection in some individuals did not alter much. Ophthalmic symptoms were cured completely in 87% cases within one year of exposure. Gastric symptoms were also relieved. Incidence of impaired memory and concentration, joint pains and easy fatigability actually increased in the follow-up years. At the end of 4 years 4 of the 250 patients had died.

Chest Radiographs

Retrospective analysis of chest radiographs taken soon after the exposure showed evidence of pulmonary oedema in 52 (31%) in the acute phase. Subsequently, 66% of these developed interstitial lesions. At the end of follow-up, 168 chest radiographs were interpreted as: normal (12%), interstitial opacities (56%), prominent B-V markings (18%), emphysema and honey combing (4%), tuberculosis (4.7%), cardiac abnormalities (5.3%). Follow-up studies showed no significant change in 72% cases, deterioration in 20% and improvement in 8% cases.

Pulmonary Function, Arterial Blood Gases and Exercise Test Studies (250 cases)

Initial spirometry test results analysed on the basis of 80% level of normalcy for FVC and 75% for FEV1 showed: normal (37.6%), airflow obstruction (19.6%), restrictive impairment (14.8%), obstructive-cum-restrictive (28%). Mean diffusion capacity of lungs (DLCO) was close to normal.

Follow-up studies of 168 cases showed a significant increase in FVC at 2nd year, remaining constant after that. FEV_1, TLC, and diffusing capacity (DLCO) remained constant throughout the follow-up period. The residual volume on the other hand showed a gradual decline (significant at 3rd and 4th year, $p<0.05$). Annual FEV_1 decline in 123 non-asthmatic cases with bronchoreversibility of <10% was more than 50 ml per year in 24 cases – including young as well as older age groups suggestive of increasing airway obstruction.

Baseline study in 208 subjects showed arterial blood oxygen tension to be normal in 140 cases, lower than 60 mm Hg (respiratory failure) only in 6 (2.8%) cases, 60-80 mm Hg in 62 (30%) cases, $PaCO_2$ >45 mm Hg was seen only in 5 (2.4%) cases.

Exercise test in 50 gas exposed cases showed significantly lower maximum oxygen uptake during treadmill exercise, compared with age, sex matched controls. Dyspnoea index VEmax/MVV%) was found to be elevated in the exposed group.

Disease Patterns

The following disease patterns were identified: airflow obstructive (20%), reactive airway dysfunction syndrome i.e. RADs (12%), restrictive lung disease (6%), small airway disease – a substantial number of cases.

Sequelae

The following sequelae were observed.
Cor-pulmonale and respiratory failure – 5 (3%)
Recurrent chest infections – many cases
Interstitial lung disease with fibrosis – 2-5% cases.

Conclusions

Five-year follow up study of 250 symptomatic, gas exposed subjects showed relief of respiratory symptoms initially over 1 year followed by constant pattern in 70% cases. Chest radiographs improved or showed no change in 72% cases, but deteriorated in 20% cases. Pulmonary function improved initially and remained stable in most cases. Exercise test showed reduced oxygen uptake. Four out of 50 patients died.

Number of Tables: 6.1 to 6.13

Chapter 7

Disproportionate symptoms in MIC/toxic gas exposed population, pulmonary function tests, blood gases and urinary thiocyanate excretion

Objectives

To understand the mechanisms underlying respiratory and other symptoms, and try modalities of treatment to ameliorate them with special reference to i.v. sodium thiosulphate (NaTS).

Investigations Carried Out

1. Estimation of Hb and its N-carbamoylation, measurement of arterial and venous blood gases, 2-3 DPG levels in blood.
2. Assessment of cyanide pool in the body by measurement of urinary thiocyanate excretion before and after provocative dose of NaTS.

Study Period

Short term study: 1985-1986
Long term ICMR cohort study: 1987-1990
Short Term Study

Oxygem Transport and Utilization by Tissues

Haemoglobin. Out of the 140 blood samples of severely exposed, symptomatic patients, 98 (70%) had >12gms Hb% levels.

N-Carbamoylation of Hb. There is unequivocal evidence in literature that on entering the blood, MIC caused N-Carbamoylation, irreversibly, of end-terminal valine residues of Hb. In the toxic gas exposed population, this would result in increased affinity of Hb for oxygen, therefore diminished unloading in tissue, to produce tissue anoxia. Simultaneously, the CO_2 transport in blood would be impaired.

2-3 DPG (diphosphoglycerate). Twenty-five of the 28 blood samples showed raised values (>2.5 n moles), suggestive of oxygen lack.

Arterial and Venous Blood Gases

Of the 15 patients, 13 showed PaO_2 between 60-80 mm Hg, and two showed <60 mm Hg, i.e. respiratory failure. The $PaCO_2$ ranged between 26.6 to 44.8 mm Hg. Peripheral venous blood showed PCO_2 45-70 mm Hg, not significantly different from that of mixed venous blood collected by right heart catheterization. The blood gas data did not explain dyspnoea experienced by the patients.

Assessment of Cyanide Pool

The role of HCN (hydrocyanic acid) in the body of toxic gas exposed population was investigated before and after i.v. administration of NaTS (10 ml, 10%) in patients who continued to be seriously ill for more than 6 weeks despite intensive treatment. Several clinical trials - including double blind - in approximately 350 patients including 50 children showed the following results.

The symptoms of breathlessness, easy fatigability and loss of work capacity were improved in a majority of patients. The symptoms of burning sensation in epigastrium, muscle and joint aches, loss of memory and black spot in vision however did not improve.

Majority of patients excreted much higher than normal concentration of thiocyanate in the urine. After six injections the excretion stabilized.

It was observed that even six months after the gas exposure the patients benefited clinically.

These findings suggested that MIC and its breakdown products (HCN etc.) had entered the blood stream and tissues and were possibly releasing toxic breakdown products in the body which affected the Hb, oxygen utilization by tissues; NaTS produced symptomatic improvement described above. These products could be only removed as urinary thiocyanate by using a "sulphane donor" such as NaTS. These findings indicated increased cyanide pool in the body which supports evidence of cyanide poisoning.

LONG TERM ICMR COHORT STUDIES (1987-1990)

Study Sample

Patients who clinically showed evidence of severe exposure to toxic gas were studied by routine clinical examination, urinary thiocyanate excretion measurement, pulmonary function tests and chest radiographs.

Urinary Thiocyanate Excretion Study
The urinary thiocyanate excretion data (1987-90) showed that there was gradual lowering of urinary thiocyanate to less that 1 mg% in 1987-88 compared with previous years. There was no significant trend seen in 1988-89, meaning that the cyanide pool in the body had more or less stabilized.

Pulmonary Function Studies (n=232)
In 1986-87, 93% patients showed abnormal pulmonary function and 7% were normal. In 1989-90, 71% were abnormal and 29% were normal. Over the years there was a shift from restrictive to restrictive-cum-obstructive pattern. Many patients with no previous history of bronchial asthma had developed asthma like symptoms. Over the year 1989-90, 190(73%) patients did not show any significant change in lung function, 28(10.8%) improved while 42 (16.2%) deteriorated.

Bronchoreversibility. In 1989-90, 102 patients were tested for broncho-reversibility with inhalation of 500 mcg salbutamol aerosol. The test was positive in 71% of them, while in previous years this was positive in 51% patients suggesting that more patients had developed asthma like symptoms.

Chest Radiography.
151 chest radiographs of severely exposed persons were analysed. In 1987-88, 36.42% were reported to be abnormal which increased to about 54% in 1988-89. Interstitial opacities were the commonest finding in 24.7% which increased to 48% after 1 year, prominent hilar shadows seen in 11% cases increased to 20% after one year.

Chest radiographs vs pulmonary function. There was a significant association between chest radiographic findings and pulmonary function status.

Blood Gas Analysis.
Arteral blood gas results of 257 patients in 1987-88 did not significantly change in 1988-89. In 123 patients, $PVCO_2$ (venous pCO_2) compared with 1984-85 results, showed a downward trend.

Conclusions
In a group of symptomatic, severely exposed patients, serum 2-3 DPG levels were found to be raised, suggesting lack of oxygenation of tissues.

Intravenous administration of sodium thiosulphate significantly relieved respiratory and neuro-psychiatric symptoms. This also produced higher than normal urinary thiocyanate excretion. Repeated course of injections stabilized thiocyanate excretion to a normal level.

The above findings suggest that the toxic gas had entered the blood stream which increased the cyanide pool in the body.

Number of Tables: 7.1 to 7.13

Chapter 8
Sequential respiratory, psychologic and immunologic studies in relation to MIC/ toxic gas over two years

Objectives
To investigate the pattern of toxic gas related lung disease by clinical and pulmonary function studies.

Study Sample (Study Period: 1985 – 1987)
One hundred thirteen patients – 77% males and 23% females, of all age groups, from the severely affected area of Railway Colony reported at KEM Hospital, Bombay for study, 7-90 days after the gas exposure initially; and at 3,6,12, 18 and 24 months thereafter.

Symptoms
1. **Respiratory.** Frequency of post-exposure symptoms were dyspnoea (97%), cough(98%), chest pain (69%), expectoration (42%). In the follow-up all symptoms showed amelioration, except dyspnoea on exertion.

2. **Neuro-psychiatric.** Muscle weakness and poor memory showed worsening with time, concentration was variable. Psychiatric assessment showed that only 19-27% of the patients were normal. The proportion with pure anxiety or depression increased over two years but those with pure lesions decreased ($p<0.05$). Hamilton scoring revealed that the proportions with normal scores for both anxiety and depression reduced over the next two years ($p<0.05$).

Chest Radiography

Chest radiographs in 96 to 98% cases showed abnormalities .The most common findings were interstitial deposits – linear, punctate, reticular, reticulo-nodular, followed by overinflation (15%), pleural and parenchymal scars (21%). In 58% these lesions showed improvement, but in 12% showed worsening at follow-up.

Pulmonary Function, Arterial Blood Gases and Exercise Test

Spirometry test results (FVC, FEV_1, expiratory flow rates) showed mainly restrictive pattern, small airway narrowing with little bronchoreversibility. Exercise test showed difficulty of oxygen exchange. The latter improved at 3 months, and spirometry test findings including expiratory flow rates improved over 12 months, only to lose some of the improvement at 24 months. Mean values of arterial blood gases and pH remained within the normal range upto 24 month follow- up. Abnormal levels of Carboxyhaemoglobin and Methaemoglobin returned to normal in the follow-up period.

Fibreoptic Bronchoscopy

Eight fibreoptic bronchoscopies showed distorted airway lumen, muscosal swelling, lymphoid hyperplasia, ulceration and patchy congestion, BAL examination showed high total cell count with neutrophil excess (4) macrophage increase (2) eosinophil excess (1) and lymphocytosis (1).

Overall Follow-up Assessment

On follow-up, only 18 to 48% of the 113 patients were clinically stable while 18 to 50% clinically were fluctuating. In the case of ventilatory functions, 17 to 32% were fluctuating.

Pathologic and Immunologic Studies

Lung histology in 3 open biopsies showed septal and pleural fibrosis, perivascular and peri-bronchial fibrosis, active bronchitis, inflammatory interstitial exudate, and interstitial scarring .

Conclusions

In a group of 113 patients – severely exposed to toxic gas – almost everybody suffered from severe breathlessness and cough; 75% of them had psychiatric symptoms. The chest radiographs showed parenchymal and bronchial involvement; spirometry tests showed pulmonary function impairment. With time they showed signs of recovery but in a small percentage of cases, these were progressive or fluctuating. Fibreoptic bronchoscopy and open lung biopsy in a few cases showed evidence of inflammatory and ulcerative lesions in bronchi and lung parenchyma.

Number of Tables: 8.1 to 8.10

Chapter 9

Pregnancy outcome in women exposed to MIC/toxic gas

Objectives

To study the effect of toxic gas on the pregnancy outcome.

Study Sample (Study Period: 1985 – 1986)

The adverse effects of toxic gas on pregnancy outcome were evaluated in 2566 women from 10 affected areas, in comparison with 1218 women from 9 control/ unexposed areas. Women from the affected area were verified to be pregnant on the day of the exposure, i.e. 3rd December 1984, while women from the control area were identified to be pregnant on 3rd December 1985. They all belonged

to poor socio-economic strata, 40.3% women in the affected areas were Muslims with 15.6% consanguinity; the corresponding figures in the control areas were 14.4% and 6.7% respectively.

Abortions

The number of pregnancies considered at risk of spontaneous abortion were 1468 and 485 in the "affected and control areas" respectively. The actual abortions recorded, however, were: 355 (24.2%) in the "affected areas" and 27 (5.6%) in the "control areas", the difference being statistically significant. Besides, the number of "induced abortions" were 26 and 03, and intermediate foetal deaths 32 and 8 in the "affected and control areas" respectively.

Deliveries

A total of 2153 and 1180 deliveries took place in the affected and control areas respectively. Of these 56 (26 per 1000) and 27 (22.9 per 1000) were "still births" in the "affected and control areas" respectively. There was no statistically significant difference in the two groups.

Live Births

The number of live births, including twin births were 2117 in the affected areas and 1160 in the control areas.

Perinatal and Neonatal Mortality

Total number of perinatal deaths per 1000 births were 69.5 and 50.5 in the "affected and control areas" respectively. The difference was statistically significant ($p<0.01$), the number of neonatal deaths per 1000 live births were 61.0 and 44.8 in the "affected and control areas" respectively. The difference was highly significant ($p<0.001$).

Congenital Malformations

The incidence of congenital malformations per 1000 births was found to be 14.2 (affected) and 12.6 (control), the difference was not statistically significant. Religion and consanguinity were not found to be associated with the pregnancy outcome.

Conclusions

The incidence of spontaneous abortions, perinatal and neonatal mortality were significantly higher in the toxic gas affected areas than the control areas. However, there was no significant difference in the incidence of congenital malformations.

Number of Tables: 9.1 to 9.6

Chapter 10

Health effects of MIC / toxic gas in children
Follow-up studies in children 0-5 years of age at the time of exposure
Study of pulmonary effects of toxic gas in children 6-15 years of age at the time of exposure

Objectives

I. To study the health effects of toxic gas inhalation in children 0-5 years old
II To study pulmonary effects of toxic gas in children 6-15 years old

I. Health Effects in Children 0-5 Years Old at the Time of Gas Exposure

Study Period: October 1986 to December 1990

Study Sample

Health effects of MIC/toxic gas were studied in 1412 children from severely affected areas who were actually exposed to gas, compared, with 1268 children from control/ unexposed areas. The two groups were equally distributed for age, gender and socio-economic strata. Data on health effects were collected through monthly morbidity surveys.

Symptoms and Signs
Prominent symptoms observed in order of frequency were: cold/running nose, cough, fever, breathlessness and gastro-intestinal (loose motions, vomiting, pain). Infections and rashes were significantly more in the "affected group" compared with "controls". Similarly, hepato–splenomegaly, rhonchi and crepts in chest were significantly more in the affected than the control group. By the third year of observation, many of these abnormalities had diminished in frequency in the affected children - except cold, cough, fever, splenomegaly and rhonchi and crepts in chest, which did not show much improvement.

Infections
The incidence of upper and lower respiratory tract, gastro-intestinal and ear, eye and skin infections were found to be significantly more common in the affected group than the control group.

Anthropometry
The weight, length and height of children in the two groups did not show any significant differences.

Conclusions
By the end of 14th morbidity round in 1988, 42% of the affected children were healthy and 44% were still suffering from morbidity; the corresponding figures for the control group were 69% and 22%. Overall, the affected group did not show evidence of progressive morbidity.

II. PULMONARY EFFECTS IN CHILDREN 6-15 YEARS OLD AT THE TIME OF GAS EXPOSURE

Study Period: April 1986 to August 1987

Study Sample
One thousand six hundred one children from severely "affected areas" and 1436 children from "control/unexposed area" were studied. Age, height, gender and socio-economic strata of the two groups were comparable.

Symptoms and Signs
Prominent symptoms and other features at the time of gas exposure were cough, breathing difficulty, choking feeling (98%); eye symptoms (99%); loss of consciousness (30%). One to 1½ years after the gas exposure, the frequency of symptoms in the affected group had reduced to nearly one third of original, but still was more than in the control group.

Pulmonary Function Tests
Peak expiratory flow rate in 796 children from "affected" and 401 "control" group did not show any significant difference. The mean values of FVC and FEV_1, in 437 boys and 359 girls in the affected group were significantly ($p<0.05$) lower than 212 boys and 189 girls in the "control group".

Conclusions
In 6-15 year old children, respiratory symptoms showed improvement with time but were still more frequent in the affected areas than the control areas. Pulmonary function also was more impaired in the affected areas than control areas.

Number of Tables: 10.1 to 10.19

Chapter 11
Mental health studies in MIC/toxic gas exposed population at Bhopal

Objectives
To study mental health of the gas affected population.

Study Groups and Study Periods [Initial assessment (February, 1985)]
It was estimated that approximately 50% of people in the toxic gas exposed community had mental health problems.

Psychiatric Evaluation (February – May 1985)
A psychiatric team made random visits to 10 clinics in the city of Bhopal and screened 855 patients. Prevalence rate of psychiatric illness was found to be 22.6%, 74% of them were females <45 years old. The main diagnostic categories were: anxiety neurosis (25%), depressive neurosis (37%), adjustment reaction with prolonged depression (20%) and adjustment reaction with predominant disturbance of emotions (16%).

Neurological Studies – (3rd Month Post-disaster)
A total of 129 adults and 47 children were studied. Three adult patients had evidence of central nervous system involvement: one each of stroke (died later), encephalopathy and cerebellar ataxia. There were six cases of peripheral nervous system involvement, 4 of vertigo and hearing loss, 50% of them gave history of loss of consciousness. Additionally, there were many cases of muscle weakness, tremors, vertigo, ataxia and easy fatigability. Most of neurologically affected cases recovered after a period of time. Of the 47 children, 50% gave history of loss of consciousness, 3 of fits and 1 of mental regression. No abnormality was found on neurological examination in children.

Research Investigations: 1. Adults 2. Children

1. ADULTS

Obectives
To study prevalence of psychiatric disorders and their associated factors.

To carry out rotational prevalence surveys annually (2nd, 3rd, 4th, and 5th year) on independently drawn samples.

Study Sample
Random sample of 700 families from each of the severe, mild exposed, and control areas were taken up for study. Information on mental health item sheet and on semi- structured proforma regarding psychiatric history, personal history, pre-morbid personality, etc were recorded.

Prevalence of Mental Disorders
The psychiatric disorders were 5 times more common in the severely exposed population – compared with control population, the mildly exposed area falling in between the severely exposed and control population. The differential between the three areas continued throughout 5 years. There was a gradual reduction in prevalence rates over 5 years at the end of which the exposed areas still had three times more prevalence rates than control areas.

Gender distribution. The prevalence rates were higher in females than in males.

Income status. In the initial survey, the lower income groups had greater tension, anxiety, depression and other psychiatric disorders than those who were economically better off. In the first and second rotational survey the psychiatric morbidity prevalence rates were higher among the higher than the lower income groups, which again reversed during the third rotational survey.

Religion. The psychiatric morbidity prevalence rates were found to be higher in Muslims than Hindus in almost every rotational survey.

Age distribution. The prevalence rates of psychiatric morbidity in the exposed area during initial survey was higher in the age group 36-45 years (166/1000), followed by 45-55 years (158/1000) and 26-35 years (134/1000). During the following rotational surveys the morbidity rates were higher among the middle aged.

Educational level. The psychiatric morbidity was not related to the education level of people.

Occupation. The phychiatric disorders were more prevalent in housewives than any other occupation.

Diagnostic break-up
At the 5th year rotational survey, it was found that 100 out of 164 patients were still suffering in the "severely exposed group", 80 out of 97 in the "mild group" and 21 out of 39 in the "control group". Initially, the numbers who were suffering were 279 severely exposed, 148 mildly exposed and 47 in controls. At the end of the 5th rotational survey, the largest number of patients had neurotic depression, followed by anxiety state *etc.* more in the severely exposed area than mildly exposed area.

2. PILOT PSYCHIATRIC STUDY OF CHILDREN (0 – 16 YEARS)

Objectives
To compare the frequency and type of psychiatric disorders and intellectual level of 0-16 years old in 100 families from a severely exposed area, compared with 100 families from one control area.

Study Sample
252 children from exposed area and 241 children from control area were included in the study.

Prevalence of Psychiatric Disorders
The prevalence rates of psychiatric disorders were 12.66 % and 2.4% in the "exposed and control areas" respectively. Enuresis, unsocialised disturbance of conduct, specific developmental delay in speech, and mental retardation were the most common disorders. The commonest symptoms in both the affected and control areas were enuresis, stubbornness and temper tantrums. The prevalence rates were higher in the "exposed group" than the "control group".

Intellectual level. The children from exposed areas had significantly lower intellectual levels than those in the control areas. The trend was not clear cut in <5 years age group.

Conclusions
In the immediate post-exposure period, nearly 50% of the population including children suffered from mental health problems. Most of them recovered.

Five years follow-up studies revealed that the prevalence rates of psychiatric disorders were several times higher in the "exposed areas" than "control areas". These were higher in women than men, as also in higher than lower age groups. Though reduced, prevalence rates were still 3 times higher in exposed areas than control areas. Number of Tables: 11.1 to 11.12.

CHAPTER 12

Follow up study of ocular changes in MIC / toxic gas exposed population of bhopal on long term basis

Objectives
To estimate the prevalence rates/incidence of specific ocular morbidities by conducting annual surveys, in Phase I and Phase II..

In- depth studies to determine the extent of morbidities, by doing detailed examination of the anterior and posterior segments in Phase II.

Acute Phase Management
Every exposee to toxic gas suffered from acute ocular symptoms, like foreign body and or burning sensation, excessive lacrimation, blurring of vision etc. About 60-70% showed conjunctival and circum-corneal congestion. In some cases superficial corneal ulcers could be seen. They were successfully treated with washing the eyes, application of antibiotic ointment, and dilating pupils with atropine if necessary

Long Term Follow-up Studies
Phase I: From March 1985 to August 1988
Phase II: From September, 1988 to September, 1992

PHASE I

Study Sample

A total of 9465 subjects from 'exposed areas' and a control sample of 3710 subjects from unexposed areas were studied. Statistical analysis of data from the two areas was done, using the test of proportions (Z test).

Ocular Morbidities

1. **Trachoma and chronic irritative conjunctivitis.** These were considered to be toxic gas exposure related. The prevalence rates of both were found to be significantly higher in the 'exposed areas' compared with 'control areas'. These changes increased with age. After 3-4 years, although the prevalence rates decreased, these remained significantly higher in the exposed group.
2. **Conjunctival xerosis.** A feature of hypovitaminosis, prevalence rates of conjunctival xerosis were higher in control areas compared with exposed areas. After 3-4 years an increase in both areas was found.
3. **Corneal involvement.** The prevalence rates of corneal involvement, including corneal opacities, in the 'exposed areas' were nearly three times more than in the 'control areas'. Band-shaped keratitis was characteristic of the toxic gas hitting the palpebral fissure of partially closed eyes. Corneal oedema was also found to be slightly more common in the exposed areas.
4. **Lenticular opacities.** In the exposed areas, the prevalence rate of lenticular opacities was 8.7% and significantly higher compared with 2.6% in the control areas. In the 'exposed group' a higher proportion of cases in 45 to 59 age group indicated early onset of cataract. Polychromatic lustre seen in some cataracts in the exposed group suggested that cataract was of a complicated nature. The incidence of cortical type was higher than nuclear type of cataract.

Fundus pathology

Prevalence rates of fundus pathology, with age-related trends, were higher (6.7%) in the "exposed group" than in the "control group" (3.0%).

Study of corneal endothelium. 'Specular microscopy' for detailed examination of corneal endothelium was carried out in 75 cases from 'exposed areas', and compared with 30 normal controls. The mean cell density in the exposed group was found to be less, compared with controls. In the exposed group, 36 cases with corneal opacities had mean cell density still lower than the rest of the exposed group. Eleven (30.55%) of the 36 cases had polymegathism of which 9 (25%) showed guttata and 3 (8.33%) had pigments, with higher incidence than the control group. Out of the 75 cases in the exposed group, polymegathism was found in 21 (28%), compared to 6 (20%) out of 30 cases in controls; guttata was observed in 14 (18.66%) exposed vs 8 (26.6%) in the control group, pigments were seen in 4 (5.3%) cases in the exposed group.

PHASE II STUDY

Objectives

- Prevalence study repeated after an interval of 3-4 years.
- In-depth studies.

Study Sample

Out of a sample of 9114 persons available, 4946 were actually studied, consisting of 1377 (27.8%) severely exposed, 1288 (26.0) moderately exposed, and 1227 (24.8%) mildly exposed, along with 1054 (21.3%) unexposed/controls.

Trachoma and chronic irritative conjunctivitis. The prevalence rates of these two conditions in phase II were lower than phase I, for both the exposed and control groups. The rates, however, continued to be higher in the former group than the control group.

Conjunctival xerosis. When compared with Phase I data, prevalence of conjunctival xerosis showed an increase in the exposed as well as the control group in Phase II. This may be due to decline in health care facilities.

Corneal involvement. The prevalence of corneal involvement was greater in Phase II in both the exposed and control groups, compared with Phase I. This suggests continuing corneal involvement with deterioration. In the exposed group, a higher proportion of persons had corneal opacities as compared to controls, in Phase II than Phase I. Over time, the prevalence rates remained unchanged in the exposed group although there was a rise in the controls.

Lenticular opacities. In Phase II the prevalence rate of cataract was significantly higher in the total exposed group compared with controls. In the 45-59 years age group, a significantly higher prevalence (33.6%) was observed as compared with controls (19.7%). This suggests early onset of cataract with polychromatic lustre. In the exposed group a slight decrease in the prevalence of cataract was recorded in Phase II (11.0% as compared to 13.3% in Phase I) whereas in the control group it remained almost similar.

Fundus abnormality. In Phase II the prevalence rate of fundus abnormality decreased in the exposed areas, whereas in the control area it increased. This, however, is believed to be not related to gas exposure.

IN–DEPTH STUDY - PHASE II

Objectives

The aim of in-depth study was a repeat of detailed ocular examination of all persons detected to have ocular abnormalities in phase I, compared with 20% controls

Study Sample

Both the eyes of a total of 864 persons i.e. 1728 eyes were examined in two Phases with a gap of about 2 years.

Observations

Trachoma. Four grades of trachoma were identified: a) G-1, active trachoma, including incipient trachoma; b) G-2, established lesions; c) G-3, healing lesions, d) G-4, healed lesions. In Phase I, 1174 eyes were normal whereas in Phase II 1169 eyes were normal. Within the abnormal group, 78 eyes showed healed lesions in phase I and 165 healed lesions in phase II. This is suggestive of beneficial results of therapy.

Chronic irritative conjunctivitis. A marked increase in number of eyes with no conjunctivitis was observed in Phase II, compared with Phase I, indicating diminishing effects attributed to toxic gas exposure.

Corneal abnormalities. A deterioration in corneal involvement was observed in Phase II compared with Phase I.

Corneal opacities. All three types of corneal opacities, viz., nebular, macular and leucomatous were found to be greater in Phase II compared with Phase I, indicating deterioration over time**.**

Lenticular opacities. An increase in the number of cataracts was observed overtime (561 in phase II vs 428 in phase I). Also, in phase I, 348 (81.3%) cataracts were of senile variety. In phase II, 351 (62.6%) were observed to be of senile variety. This indicates that 19% and 37% cataracts were of complicated type in Phase I and II respectively. Polychromatic lustre was observed in some of these by slit lamp examination.

Conclusions

The long term ocular morbidity studies showed that the toxic gas exposure resulted in irreversible ocular changes namely trachoma, chronic irritative conjunctivitis, corneal opacities, cataract– complicated in some cases with polychromatic lustre and fundus abnormalities.

Number of Tables: 12.1 to 12.25

Chapter 13

Study of oral mucosal gingival and orodental anomalies in children whose mothers were exposed to MIC / toxic gas during pregnancy

Objectives

To study mucosal, gingival and oro-dental anomalies in children born to mothers who were exposed to MIC/toxic gas during pregnancy.

Study Period

November 1986 to June 1991.

Study Sample

Initially, 1216 children from affected and 663 children from unaffected/control areas were included in the study. Later, in 1987, 801 more children were included.

Observations and Conclusions

1. No congenital malformation of face and arches could be seen in the affected group compared with control group.
2. No significant changes were observed in oral mucosa, gingivae and tongue in both the affected and control groups. Fifty-six children, however, of the affected group showed ulcers on tongue, labial mucosa, floor and angle of mouth, but these disappeared spontaneously.
3. No numerological, morphological, visual, histological anomaly or discoloration were noted in the affected or control population.
4. No significant difference in the eruption trends were noted in the two groups.
5. Facial heights and bizygomatic width showed very slight difference in the affected and control groups. The affected group seemed to be slightly behind, compared with the control group.

Chapter 14

National cancer registry programme (Indian Council of Medical Research) Cancer Patients in MIC/Toxic gas affected and unaffected areas of Bhopal (1988-2003)

Objectives

Registration of all cancer cases of residents of Bhopal and generate a data base.

To observe and compare the incidence rate of cancer (all sites) in MIC/toxic gas affected and un-affected areas of Bhopal.

To assess the time trend in the incidence of various types of cancer in the two areas.

Data Collection

Under the National Cancer Registry Programme (NCRP), the Indian Council of Medical Research (ICMR) set up a Population Based Cancer Registry (PBCR) in Bhopal. Data collection started from January 1, 1988. The cases born after 1985 were excluded from further analysis. The incidence rates for the year 1988 to 2003 were subjected to regression analysis.

Observations and Conclusions

The data on patterns and trends of cancer in the Bhopal PBCR have shown some differences between the population in the areas exposed to MIC/toxic gas and those that were not exposed. The higher incidence rates of sites of cancer in the gas affected areas are all those anatomical sites that are associated with use of tobacco. Such differences could be due to confounding factors as there are variations in the tobacco habits and socio-economic status of the population in the two areas. At this state, the two different groups of cancer cases can not be causally attributed to MIC.

Chapter 1

Early Observations Including Clinical, Radiological and Pulmonary Function Studies in MIC/Toxic Gas Exposed Population in the Acute and Subacute Phases

ACUTE PHASE

Clinical records of 978 patients admitted to the Hamidia Hospital, Bhopal, soon after the MIC toxic gas leak on December 2-3, 1984, were analysed to document the acute effects of the toxic gas on human health[1,2]. Genderwise, 458 (46.8%) were males and 520 (53.2%) were females.

Seven hundred and thirty-three of the 978 patients lived in areas within 1 km of the Union Carbide Factory, 127 were from within 1-2 km and the remaining 118 were from areas situated more than 2 km away from the factory. Residents of a colony situated adjacent to the factory but in opposite direction of the wind on that fateful night largely escaped the effects of exposure to the toxic gas.

Of the 978 patients, 812 had rushed out of their homes and ran in different directions. Most patients belonged to the lower socio-economic strata and lived in hutments or houses devoid of any windows or proper shutters and therefore were un-protected against the entry of the toxic gas. Some of the inhabitants living in well constructed houses in the same area had shut their windows because of the cold night and suffered less severe exposure and therefore did not experience much serious symptoms. Those who covered their faces with a wet cloth and also covered themselves under the impression that they were exposed to tear gas also escaped severe symptoms. All the hospitalized patients were symptomatic and suffered from severe symptoms mainly pertaining to eyes and respiratory system. Exposed persons described that the gas had a 'peculiar' odour which was so unfamiliar to them that it could not be equated with any other common or familiar smell.

Out of the 978 patients admitted into the hospital, clinical records of 544 patients were found to be complete to permit a proper statistical analysis of data. The results are presented in Tables 1.1 and 1.2.

Table 1.1 Acute Symptoms Experienced by 544 Patients Exposed to Toxic Gas

Symptoms	No. of patients
Respiratory symptoms	
Breathlessness	538 (98.89)
Cough	516 (94.84)
Presence of pink froth at mouth	283 (52.00
Irritation in throat/choking	250 (45.95)
Pain in chest	136 (25.00)
Expectoration	87 (15.99)
Haemoptysis	66 (12.60)
Hoarseness	11 (2.00)
Gastro-intestinal symptoms	
Loss of appetite	499 (91.70)
Nausea/retching/vomiting	283 (52.00)
Epigastric discomfort	103 (18.90)
Diarrhoea	66 (12.60)

Eyes	
Irritation/lacrimation/blurring of vision/foreign body sensation	467 (85.80)
Neurological symptoms	
Extreme weakness (myasthenia – like)	136 (25.00)
Apathy, listlessness	119 (21.87)
Hypersomnolence	87 (15.99)
Coma	40 (7.20)
Tremors	11 (2.00)
Tetany	5 (0.9)

Figures in parentheses are the percentage values

Table 1.2 Physical Signs in Patients Exposed to Toxic Gas – Acute Phase

Physical Sign	No. of Patients
Pulse rate	
Tachycardia (above 100/min)	294 (54.00)
Bradycardia (below 60/min)	6 (1.20)
Respiratory rate	
Below 20/min	66 (12.12)
Between 20-40/min	324 (59.52)
Above 40/min	110 (20.24)
Gasping	44 (7.12)
Temperature	
Afebrile	531 (97.63)
Febrile	13 (2.42)
Lung findings	
Rhonchi and crepitations	452 (83.08)
Pleural rub	7 (1.23)
Normal	86 (15.82)

Figures in parentheses are the percentage values

The most prominent symptoms and signs shown in Tables 1.1 and 1.2 reported by the exposees were choking sensation and breathlessness, a sense of extreme weakness, vomiting, and irritation of the eyes[2]. The limbs felt flaccid and few had fasciculations and tetanic movements. However, the typical cyanotic tinge was conspicuous by its absence. Rhonchi and crepitations were heard in the lung in most patients. Electrocardiograms did not show significant abnormality during the acute phase. Chest x-rays revealed evidence of diffuse non-homogeneous opacities mostly localized in the mid and lower zones, ground glass opacity involving all zones, and punctate, linear and micro-nodular opacities. There were marked radiological clearing in most of the cases by the end of two weeks.

Ocular symptoms caused by toxic gas contact were similar to that produced by any weak acid, producing severe burning, foreign body sensation, lacrymation, photophobia and blurring of vision - severity of manifestations presumably depending on duration of exposure and concentration of toxic gas in the atmosphere. Mild cases only showed conjunctival hyperaemia but in severe cases marked photophobia, blepharospasm and palpebral edema were present, with kerato-conjunctivitis. Corneal lesions varied from limbal edema to large epithelial defects, the characteristic corneal lesion was a band shaped epithelial denudation in the interpalpebral area. Mild iritis was reported in a few cases. The pupils were constricted in most cases with poor reaction to light (see Chapter 12).

Of the 978 patients admitted in Hamidia Hospital, 70 (7.1%) died. Early deaths were due to respiratory failure and deaths on subsequent days were also due to respiratory complications. The patients were managed on conservative lines such as oxygen administration, bronchodilators, steroids and antibiotics. It had been observed that a high dose of steroids (e.g. 1 G methyl

prednisolone given as an intravenous drip) was most effective in controlling symptoms. Some severely ill patients were mechanically ventilated.

Of the 193 (19.6%) patients with psychiatric symptoms following the acute episode, 37.3% were suffering from neurotic depression, 24.9% from anxiety state and 35.2% from adjustment reaction[3].

Radiological investigations[4] of 500 cases soon after the gas leak revealed interstitial edema (41.4%), interstitial with alveolar edema (40.6%), pneumonitis, cavitation, pleural effusion (8%), pre-existing lung diseases like tuberculosis, COPD etc. (7.2%), unilateral opaque lung (0.6%), no abnormality (2.2%). Radiological lesions gradually cleared with passage of time in most of the cases leaving streaky, nodular, punctuate and reticular shadows in some cases (for details see Chapter 3).

Eighty-two patients exposed to the toxic gas, from the Railway Colony, who presented at KEM Hospital, Bombay within 7 to 90 days of the exposure were investigated there[5]. Seventy-eight percent showed a restrictive ventilatory defect. A significant improvement after bronchodilator aerosol inhalation was seen in 24 (29%), suggesting additional obstructive element. Inability to maintain normal ventilation and oxygen uptake at rest was seen in 45 cases (55%). Ability to increase the oxygen uptake (adequately) on exercise was impaired in 24 subjects. In 78 patients, there were extensive radiographic changes suggesting interstitial deposits. Flow volume studies in 35 patients showed changes in small airways in 12 (34%) and in - coordination of central airways in 15 (43%) cases. In 66 (96%) out of 69 cases carboxyhemoglobin (COHb) levels were raised and high methaemoglobin levels were seen in 63 (79%) out of 80 patients. There was no persistent abnormality of liver or kidney function (for details see Chapter 8).

Lung histo-pathology studied at a later stage in 3 cases from tissue obtained by open lung biopsy revealed : pleural fibrosis with focal mesothelial proliferation, thickened inter-alveolar septa, mononuclear infiltration in bronchial and peri-bronchial tissues, patchy peri-bronchial and peri-vascular fibrosis, destruction of bronchial wall and epithelium. No desquamation was seen. Muscular arteries and arterioles showed intimal hyaline thickening in one case, suggestive of hypersensitivity. In another patient who had a severe exposure, besides the changes described, bronchioles were full of inflammatory exudates obliterating the lumen completely with round cell infiltration, a typical picture of bronchiolitis obliterans, which may be the hallmark of the pathological lesions caused by the toxic gas. However, further studies on a significant number of cases would be required to confirm this[5].

Preliminary immunological, mutagenic and genotoxic studies[6] in gas victims in general showed inconsistent abnormalities of a minor nature except in case of cell cycle parameters, which were distinctly abnormal. There was a severe reduction in the second cycle metaphases, a delay in cell cycle and depression of proliferation of lymphocytes in response to PHA in exposed subjects. There was an increase in mean absolute number of T cells and Th cell population. There was slight increase in IgA and IgM levels but IgG levels were comparable to normal. Some exposed persons showed chromosomal aberrations and numerical variations (aneuploids and polyploids) of minor nature and frequencies of such abnormalities were within normal limits. No mutagens were detected. Sperm morphology, mobility and counts were comparable to those of unexposed subjects.

At autopsy, lungs showed marked congestion, haemorrhages and consolidation[7, 8]. There was a characteristic “cherry red” colour of venous blood, lungs were voluminous and edematous weighing 2-3 times of normal. Liver, kidneys, stomach, intestines and brain showed focal hemorrhages. Histopathology of lungs revealed congestion of parenchyma and denudation of epithelium in airways. There was evidence of tracheitis, bronchitis, bronchiolitis, extensive and

widespread edema of lungs, clearing after a lapse of time, with reactive changes taking over, resulting in bronchiolitis obliterans, with organizing pneumonia in a few. There was evidence of damage to alveolar epithelium and underlying endothelial cells in alveolar septa; proliferation of type II pneumonocyte with abundant surfactant material and varying degree of floccular degeneration of mitochondria of cardiac and other cells were seen. Liver showed varying degree of acute agonal changes. There was evidence of anoxic changes in brain. There was cerebral edema and acute nerve cell damage, with evidence of peri-cellular and peri-capillary edema. Long term exposure effects in human beings have not been reported so far. A detailed account of histopathology in acute phase and long term follow-up will appear in the Pathology and Toxicology Report, under preparation.

Clinical management in acute phase of the toxic gas induced lung disease consisted of administration of antibiotics, bronchodilators, oxygen therapy and other life support measures, cough suppressants. High doses of corticosteroids were administered in some of the critically ill patients with positive outcome. Also, systematic trials with sodium thiosulphate were carried out (see Chapter 7) with beneficial effects.

SUBACUTE PHASE

The subacute phase of the toxic gas morbidities is arbitrarily separated from the acute phase, i.e., 4 weeks after the exposure. The findings of a study of clinical, radiological and pulmonary function changes during subacute phase of toxic gas exposure are presented below.

Study Period : January to March 1985
Study population

One hundred and fifty three patients exposed to toxic gas and presenting with respiratory symptoms were studied at the MIC clinic at Hamidia Hospital, Bhopal. These were patients exposed to toxic gas, not acutely ill to require hospitalization, but had persistent cough with or without expectoration and breathlessness on exertion.

Clinical assessment and investigations of each patient included detailed history, physical examination and full plate PA chest x-ray examination. Patients with pre-existing cardio-respiratory disease were excluded from the study.

Spirometry

Spirometry was done as an outdoor procedure on portable spirometer "Vitalograph", in sitting posture and a minimum of two consistent readings were obtained. The test values were expressed at BTPS and the highest value obtained was used for analysis. The parameters calculated included:

i) Forced vital capacity (FVC), ii) Forced expiratory volume in one second (FEV1),
iii) FEV1/FVC% iv) Forced mid-expiratory flow over 25-75% (FMF 25-75%) and
v) Spirometric response to inhaled bronchodilator.

Thirty-one of the 153 patients, who had obstructive or obstructive cum restrictive ventilatory defect, were given two 'puffs' of salbutamol (200 μg) from a metered dose inhaler and spirometry was repeated 15 minutes later. The changes in FEV1 and FVC respectively were recorded and the sum of the percentage changes in FEV1 and FVC was calculated. The results were reported as no response (<15%), significant response (15-30%) and marked response (>30%)[9].

Classification of Severity of Exposure

1. **Severe exposure**. If one of the members of the family died or the patient became unconscious after exposure or the patient had severe ophthalmic and respiratory symptoms requiring immediate medical help with somebody's assistance.
2. **Moderate exposure.** If, after the exposure to toxic gas, the patient developed respiratory symptoms and required immediate medical relief.
3. **Mild exposure.** After exposure to toxic gas, if the patient developed respiratory symptoms but did not seek immediate medical relief because of the mild nature of symptoms.

Classification of Pulmonary Function Abnormalities

The basis for classification of ventilatory defect into 3 types i.e. obstructive, restrictive and obstructive-cum-restrictive[10], using the predicted normal values of pulmonary function[11, 12] was as follows :

1. **Obstructive ventilatory defect.** The ratio of measured FEV1 to measured FVC was less than 75% and the ratio of measured FVC to predicted FVC was more than 75%.
2. **Restrictive ventilatory defect.** The ratio of measured FVC to predicted FVC was less than 75% and the ratio of measured FEV1 to measured FVC was more than 75%.
3. **Obstructive cum restrictive ventilatory defect.** The ratio of measured FEV1 to measured FVC and the ratio of measured FVC to predicted FVC were both less than 75%.

Gradation of Respiratory Impairment

The respiratory impairment was categorized by pulmonary function testing as follows[14].

1. **Mildly impaired.** FVC 60% to 79% of predicted or FEV1 60% to 79% of predicted, or FEV1/FVC%, 60% to 74%.
2. **Moderately impaired.** FVC 51% to 59% of predicted or FEV1 41% to 59% of predicted or FEV1/FVC x 100 41% to 59%.
3. **Severely impaired** FVC 50% or less of predicted or FEV1 40% or less of predicted or FEV1/FVC% - 40% or less.

Small Airway Disease

In the presence of normal values of FVC, FEV1 and FEV1/FVC x 100, a reduction in forced mid expiratory flow 25-75% (FMF 25-75%) to less than 75% of predicted, was considered as evidence of small airway disease[14].

Analysis of Data

Twenty-four patients' data were excluded from analysis due to various reasons viz., old pulmonary tuberculosis(3), bronchial asthma and allergic rhinitis(2), chronic bronchitis(5), cyst in the lung(1), exposure to hydrochloric acid(1), bronchiectasis(1), insufficient information(9) and unexposed person(2).

The data of 129 patients are presented as mean ± SD. Data were analysed by student's t test. The trend Chi square test was applied to see whether the severity of exposure as defined above had any trend effect on pulmonary function.

RESULTS

There were 90 males and 39 females in the study. The mean age of the males was 34±11.5 years (range 12-70 years) and of females 30.9±10.3 years (range 12-55 years), the mean height was 1.67±0.07 meters (males) and 1.54±0.005 meters (females) and the mean weight was 52.1±12.0 kg (males) and 46.0±12.2 kg (females). There were 14 patients with mild exposure, 49 with moderate exposure and 66 with severe exposure. Thirty-two males were smokers, 17 of them said that they were smoking less than 5 cigarettes or bidis a day. Only five patients admitted smoking more than 10 cigarettes or bidis per day. Since there was no significant difference in pulmonary function test values between smokers and non-smokers, data were pooled for analysis.

All patients in this study were residents of areas within 2 kilometers of Union Carbide Factory and most lived within 1 kilometer. There were 21 patients (16%) engaged in dusty occupation such as laborers, painters, carpenters, masons, tailors, truck drivers etc. and 81 (62.8%) were engaged in non-dusty occupations (government employees, engineers, doctors, business executives, students etc.). Twenty-four females were house wives and three did not have any occupation.

Symptoms are depicted in Table 1.3. Findings on physical examination, pulmonary function tests and x-ray chest are given in Tables 1.4, 1.5 and 1.6 respectively.

Table 1.3 Symptomatology

Breathlessness on exertion	105 (80%)
Cough	95 (74%)
Chest pain	42 (33%)
Breathlessness at rest	5
Hoarseness of voice	4
Choking sensation	3
Fatigability	3
Giddiness	3
Sore throat	2
Squeezing sensation in chest	2
Fever	2
Heaviness of chest	1
Loss of weight	1
Sleeplessness	1

Table 1.4 Pulmonary Function Test Results

		Males (n=90)	**Females (n=39)**
FVC	Predicted (L)	3.90 ±0.40	2.64 ±0.23
	Observed (L)	3.34* ±0.90	2.19* ±0.90
	% Predicted	85.6 ±21.0	82.0 ±24.0
FEV1	Predicted (L)	3.08 ±0.45	2.11 ±0.19
	Observed (L)	2.63* ±0.94	1.79** ±0.68
	% Predicted	84.1 ±28.0	83.4 ±29.5
FEV1/FVC%		77.1 ±11.8	80.2 ±11.8
FMF25-75%	Predicted (L/min)	185.7 ±54.7	158.8 ±18.5

	Observed (L/min)	149.4* ±90.0	118.7* ±67.4
	% Predicted	82.8 ±43.4	74.2 ±40.9

*p<0.001, **p<0.01 as compared with predicted values

Table 1.5 Pulmonary Function Abnormality

	Normal	Obstruction	Restriction	Obstruction-cum-restriction
Males (n=90)	48 (53)	10 (11)	9 (10)	23 (26)
Females (n=39)	24 (61.5)	3 (7.7)	7 (17.9)	5 (12.8)
Total (n=129)	72 (55.8)	13 (10.1)	16 (12.4)	28 (21.7)

Figures in parentheses are percentages

Table 1.6 X-ray Chest Findings vs Pulmonary Function

X-ray findings	Pulmonary function			
	Normal	Obstruction	Restriction	Obstruction + Restriction
Reticular (n=22)	5 (22.7)	2 (9.1)	5 (22.7)	10 (45.5)
Pleural abnormality (n=3)	0	0	2 (66.7)	1 (33.3)
Raised diaphragm (n=2)	1 (50)	0	1 (50)	0
Cardiomegaly (n=1)	0	0	0	1
BV markings (n=56)	27 (48.2)	9 (16.1)	7 (12.5)	13 (23.2)
Normal (n=57)	38 (80.9)	2 (4.2)	3 (6.4)	4 (8.5)

Figures in parentheses are percentages

Severity of Exposure vs Pulmonary Function

Forty-three of 66 patients (65.2%) with severe exposure had ventilatory defect whereas none of the mildly exposed patients had ventilatory defect (Table 1.7). With increasing severity of exposure, there was a higher proportion of patients to have increasing functional impairment and this trend was statistically significant (p<0.001).

Table 1.7 Severity of Exposure Vs Pulmonary Function

Severity of exposure	Pulmonary function			
	Normal	Obstruction	Restriction	Obstruction + Restriction
Severe (n=66)	23 (34.8)	9 (13.6)	11 (16.7)	23 (34.8)
Moderate (n=49)	35 (71.4)	4 (8.2)	5 (10.2)	5 (10.2)
Mild (n=14)	14 (100)	0	0	0

Figures in parentheses are percentages

Physical Findings vs Pulmonary Function

It is observed that abnormal physical findings were associated with abnormal pulmonary function in 82% (41 of 50) of cases. It can further be observed that 20.3% (16 of 79) cases with normal physical findings had abnormal pulmonary function (Table 1.8).

Table 1.8 Physical Findings vs Pulmonary Function

Physical findings	Pulmonary function			
	Normal	Obstruction	Restriction	Obstruction + Restriction
Rales (n=27)	4 (14.8)	3 (11.1)	10 (37)	10 (37)
Rhonchi (n=8)	4 (50)	1 (12.5)	0	3 (37.5)
Rales + Rhonchi (n=15)	1 (6.7)	2 (13.3)	2 (13.3)	10 (66.7)
Normal (n=79)	63 (79.7)	7 (8.9)	4 (5.1)	5 (6.3)

Figures in parentheses are percentages

Response to Bronchodilators

None of the 31 patients assessed admitted having any pre-exposure episodes of bronchial asthma. However, one patient had a history of atopy and another had a family history of bronchial asthma. Thirteen (41%) out of 31 patients had shown reversibility to bronchodilators and 9 (29%) had marked reversibility suggesting the possibility of Reactive Airways Dysfunction Syndrome[14].

DISCUSSION

In the present study of symptomatic subjects, spirometry carried out 1-3 months after the exposure to the toxic gas revealed significant impairment of pulmonary function in 44.2% of them. The predominant type of impairment was obstructive-cum-restrictive. Majority of patients with abnormal physical findings had abnormal pulmonary function. The latter was noticed mainly in severely and moderately exposed patients, and those with mild exposure had normal pulmonary function. However, the observations that 20.3% of patients with normal physical findings and 19.1% of patients with normal chest x-rays had abnormal pulmonary function suggest that complete evaluation including pulmonary function testing is essential in all the exposed subjects who remain symptomatic.

The absence of fever and the findings that cough was associated with breathlessness and not with expectoration suggest that the respiratory symptoms in these patients may not be due to bacterial or viral infections. The fact that only 16% of patients in this study were engaged in industrial occupation and that only five subjects were heavy smokers, indicate that the respiratory symptoms and ventilatory impairment in most of them were not due to occupational/environmental exposures or smoking. The development of respiratory symptoms and the persistence of ventilatory impairment in a substantial number of subjects following toxic gas exposure and the fact that these subjects had no pre-existing lung disease prior to exposure and were residing in the vicinity of Union Carbide Factory at the time of exposure strongly suggest that their respiratory morbidity had resulted from inhalation of the toxic gas.

Even though 44.2% of patients attending the hospital with symptoms had ventilatory abnormalities, a thorough follow-up of these patients at ½ yearly or yearly intervals will only answer the question whether the ventilatory abnormalities are reversible or not. Even individuals with normal ventilatory function should be followed up to observe any progressive abnormalities developing at a later date. The finding of reversibility to bronchodilators in a substantial number of subjects without previous history of bronchial asthma and atopy suggest the possibility of Reactive Airways Dysfunction Syndrome (RADS).

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Chapter 2

*Pathophysiology of Lung Disease Caused by Inhalation of MIC/Toxic Gas Based on Serial Studies of Pulmonary Function, Arterial Blood Gases, Acid-Base and Cardio-Pulmonary Exercise Test

INTRODUCTION

The clinical[1-3], autopsy[4] and epidemiological studies[5] on the Methyl isocyanate/toxic gas affected population of Bhopal, conducted within days of the disaster, provided unequivocal evidence of the following respiratory morbidities. The MIC/toxic gas may also be referred to simply as toxic gas in this communication.

1. The toxic gas was highly reactive and all those who inhaled it instantly developed respiratory symptoms of cough with or without expectoration, breathlessness, tachypnoea, gasping, inability to do physical work, and chest pain – the severity of symptoms was presumably determined by the concentration of the toxic gas and duration of exposure. At least 2000 deaths occurred over the first 72 hours.
2. Five hundred chest radiographs of severely symptomatic patients taken within 72 hours showed evidence of extensive alveolar/interstitial oedema, streaky and patchy opacities in 98% of cases, showing signs of clearance over the following days.
3. Autopsy studies revealed evidence of extensive alveolar-interstitial oedema and hemorrhages in lungs and anoxic damage in other organs especially the brain.
4. Based on the available mortality data, the Indian Council of Medical Research (ICMR) categorized the entire region/population of Bhopal into : severely, moderately, mildly exposed; and unexposed/control areas/population.

Thus, the respiratory effects of the toxic gas were extremely alarming. As this was the first massive disaster of its kind in the whole world, and nothing was known about the nature of the toxic gas and related morbidities, nor of its antidote, and lacs of people had been affected, it was extremely important that research studies and investigations were started to understand what kind of health effects would occur in the affected popoulation. While extensive routine clinical studies were underway, a most important aspect was to carry out pulmonary function and arterial blood gas studies to exactly understand the pathophysiology of toxic gas related lung disease so that rational therapeutic and preventive measures could be undertaken. Moreover, serial studies would shed light on the future course of the respiratory morbidities; whether these lesions would show complete or partial resolution, fibrosis, or lead to progressive lung disease and even cancer, disability and death over the years to come.

While the equipment for state-of-the-art pulmonary function tests, arterial blood gases, acid-base measurements and cardio-pulmonary exercise test (CPET) were being procured, a pilot study by spirometry and arterial blood gas measurement was done on 224 patients with severe respiratory symptoms from first week of January, 1985 to mid-March, 1985. The findings were extremely interesting[6]. It was observed that while all subjects were symptomatic – most common being dyspnoea (91%) and cough (71%) – 126 (56%) of them showed normal pulmonary function test values. The rest of them had minor impairment of

*Supported by DST Centre for Visceral Mechanisms, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110007.

lung function and only 2 of the 46 arterial blood gas studies revealed PO_2 below 60 mm Hg, while none showed raised PCO_2. The highlight of the investigation was that pulmonary disability caused by dyspnoea could not be explained by clinical findings or by pulmonary function impairment[6].

Two other important observations were made : (i) the chest radiographs showed evidence of clearance[3]; and (ii) the mortality rates rapidly fell after the 3rd or 4th week of the gas disaster[5], suggestive of regression of the primary disease process.

A detailed study was planned with the objective of understanding the nature, severity and future course of chronic lung disease caused after a single exposure of healthy people to the toxic gas. A deliberate attempt was made to select a group of possibly the worst affected patients and conduct on them serial studies - over the following five years - of pulmonary function, arterial blood gases and cardio-pulmonary exercise test (CPET).

MATERIALS

Selection of Study Sample

One of us – Dr. A.Verma – who was familiar with the severely exposed/affected areas of the city, actually made a door-to-door visit of these places and identified very severely affected patients, and brought them to the Respiratory Laboratory located in the MIC Ward of the Hamidia Hospital of the Gandhi Medical College. Similarly, patients were identified from amongst the in-patients of the MIC ward. They were administered a prestructured clinical questionnaire, and also examined in detail along with the available chest radiographs and laboratory investigation reports.

Inclusion Criteria. These patients who were previously healthy were assessed on the Severity Score Scale (see Table 2.1). All patients with a 'score' of more than 10 points were included in the initial study (S1).

Table 2.1 Scoring Points to Determine Severity of Exposure to MIC/Toxic Gas: Applicable to Those who Developed Respiratory Illness Soon After the Exposure

Event	*Score points
Locality of exposure as per ICMR classification5	
Severely affected	2
Moderately affected	1
Mildly affected	0.5
Death in the family attributable to MIC/toxic gas	3
Death in neighbourhood – within radius of three houses – attributable to MIC	2
Hospitalisation	2
Disturbed consciousness lasting at least 3 hours	
Unconsciousness	2
Drowsiness	1
1st Chest radiograph	
Pulmonary oedema, reticulonodular opacities, patchy opacities	2
Linear, streaky opacities with positive physical signs in chest	1
Pulmonary oedema in the family members, currently	1
Two of the four major respiratory symptoms (dyspnea, cough, chest pain, pulmonary disability) present continuously for three months after the exposure	1

Maximum score could be 15 points.

Exclusion criteria. Patients with past history or evidence of pre-existing lung disease like asthma, pneumonia, tuberculosis, chronic bronchitis, naso-bronchial allergy, cardiac, hepatic, musculo-skeletal disease or diabetes, were excluded from the study.

Thus, a total of 119 patients were selected for study : males = 78, females = 41. At the time of gas leak they were present in the following locations : Railway Station, East and West Colony (41); Kainchi Chhola, Chhola Road (32); J.P.Colony (24); Ibrahim Ganj (5); Kazi Camp (4); Power House Bezaria (3); Chand Bad (2); Hamidia Road (2); Location not identified (6). At the time of gas exposure they were engaged in the following occupations : manual labour (17.6%); skilled labour (21.0%); office worker/shopkeeper (20.2%); housewife (27.7%); student (6.7%); and unemployed (6.7%).

METHODS

Detailed clinical history was taken and thorough physical examination was done. Pulmonary function tests; arterial blood gases, pH and cardio-pulmonary exercise test (CPET) were performed.

A state-of-the-art, Morgan Transfer Test Model C, No. 236 (60, Manor Road, Chathan Kent, England) Fig. 2.1A was used for pulmonary function studies, strictly according to the principles and methodology described by Cotes[7]. The arterial blood gases, pH and acid-base parameters were measured with IL (BGM) US micro-electrode system.

Plan of Pulmonary Function and Arterial Blood Gas Studies

1. **Static lung volumes.** These comprised of slow vital capacity (SVC), residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC) : to estimate size of lungs, shift in mid-thoracic position, and to identify obstructive and restrictive pulmonary impairment. Rolling seal spirometer and helium-dilution technique was used for FRC, RV, SVC and TLC.
2. **Dynamic lung volumes.** Forced vital capacity (FVC) and forced expiratory volume in the 1st second (FEV_1) – to detect air flow obstruction reflecting on size of central airway lumen were measured with rolling seal spirometer.
3. **Forced expiratory flow rates.** Peak expiratory flow rate (PEFR), forced expiratory flow rates at 50% (FEF50), 75% (FEF75) and mean mid-expiratory flow rate (FEF25-75%) were calculated from flow-volume loop to assess elastic properties of lungs and airway lumen size to diagnose airflow obstruction in the central and peripheral airways.
4. **Maximum voluntary ventilation (MVV)** was measured again as a test of airway lumen, elastic properties of lungs and strength of respiratory muscles.
5. **Single breath lung diffusing capacity for carbon monoxide (lung transfer factor – DLCO)**, also expressed as ml/min/mmHg per unit lung volume (KCO) measured the perfused surface area, thickness and integrity of the alveolo-capillary membrane.
6. **Arterial blood gases and acid-base parameters** measured the integrated function of ventilation, perfusion and diffusion, in the form of PO_2, Pco_2, pH and HCO_3.
7. **Broncho-reversibility test.** In all patients spirometery test (FVC, FEV_1, expiratory flow rates and MVV) was repeated after the administration of 400 μg salbutamol aerosol through spacer device in order to determine the degree of airflow obstruction reversibility.

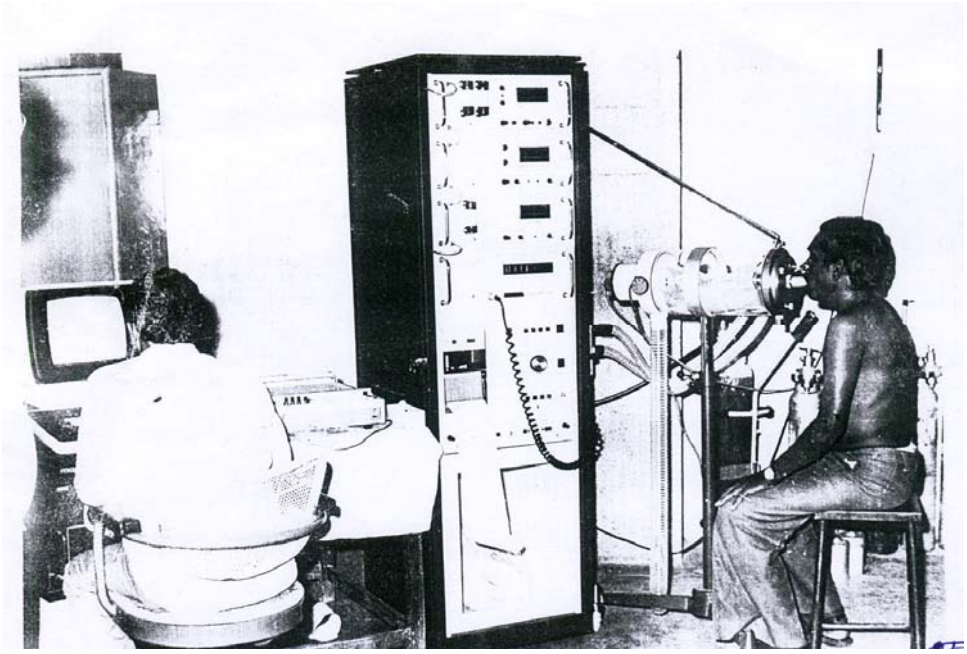

Fig. 2.1 A Pulmonary Function Test

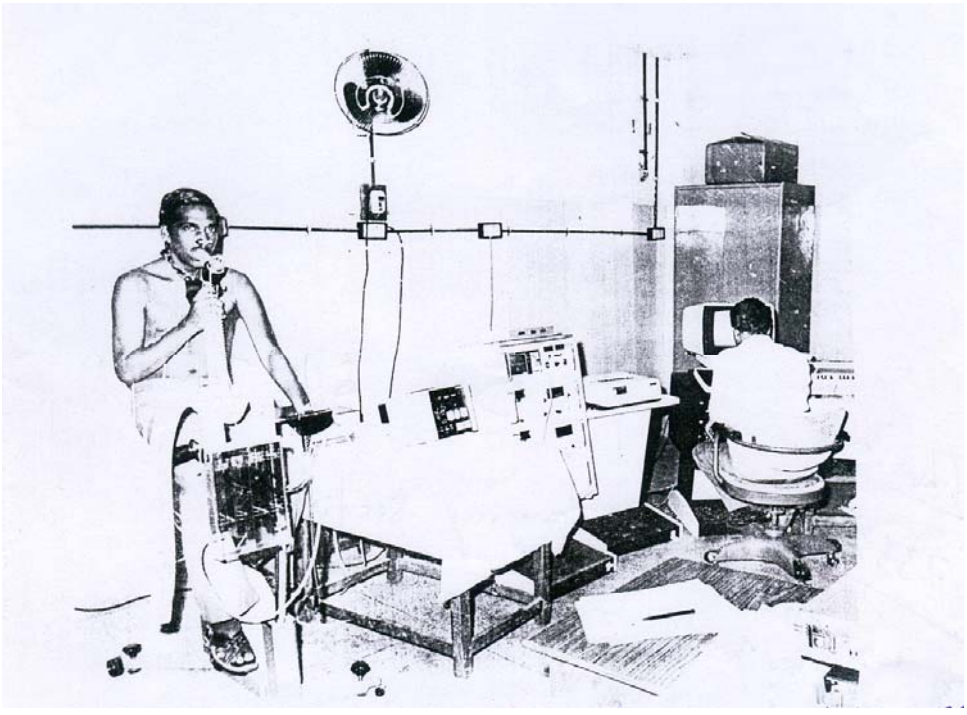

Fig. 2.1 B Cardiopulmonary Exercise Test

Cardiopulmonary Exercise Test (CPET)

Purpose

CPET was done in male patients to test aerobic work capacity, and to evaluate mechanisms underlying exercise limitation, unexplained exertional dyspnoea and pulmonary disability as to whether it is cardiac, respiratory, metabolic or psychogenic in origin. The test was

performed on 53 male patients in the initial study (S1), with P.K.Morgan Exercise Test System, Wyvern Exercise Test Software Version 7.0, (Fig. 2.1B) using standard methodology[7,8]. An electrically braked cycle ergometer was used in preference to treadmill because of simplicity of use; body weight is supported, while large leg muscle groups are used for exercise; work rate can be precisely defined and work load can be quickly changed. The patient was tested in post-absorptive phase i.e. 2 hour after breakfast or lunch - after giving him a brief explanation and "practice run" on unloaded cycle ergometer. Basically, maximum symptom-limited incremental work load (ramp pattern) was given, increasing the work load at a rate of 10 watts per minute. Heart rate, tidal volume, respiratory rate, minute ventilation, expired air oxygen and CO_2 concentration, the rate of work or power *i.e.* watts, oxygen uptake and CO_2 production per min; respiratory quotient (RQ) and derived values of various parameters were continuously recorded online every 30 seconds. ECG recorded the heart rate being averaged every 15 sec. The patient breathed through a low resistance, low dead space, transparent unidirectional breathing valve. A light weight turbine volume transducer with photocell was placed in the inspiratory side. The interruptions of a light beam measured inspired air volume[9], while the expired air was mixed in a mixing chamber before passing through infra-red CO2 analyser and paramagnetic oxygen analyzer. The lag factor was corrected. The exercise test was stopped when the patient indicated that he could go no further (see Table 2.23). VO_2, i.e. oxygen uptake was measured at the break-point of exercise; no attempt was made to measure VO_2 max.

Follow-up studies

Pulmonary function studies were repeated (S2) at least 6 months after the initial study, i.e. (S1), in 59 males and 25 females and again (S3) about 5 years after the exposure in 34 males and 12 females. Similarly, CPET study was repeated (S2) in 27 males – 18 non-smokers and 9 smokers. Patients who had gotten well were always reluctant to cooperate for follow-up studies, it was observed. All patients who were less than 20 years old at the time of initial study (S1) were excluded from the follow-up studies (S2, S3).

Analysis of data

All pulmonary function and arterial blood gas, pH, acid-base, and CPET data were analysed using the standard methods of group statistics, descriptive statistics, paired t test and 2-tailed t test. All observed values of pulmonary function and cardiopulmonary exercise test were compared with mean predicted values derived from the regression equations (adapted for Indian population) provided by the suppliers of the equipment. The regression equations for pulmonary function tests were validated for the Bhopal population (unpublished observations) as the latter did not have any regression equations (prediction formulae) of its own.

RESULTS

Study Groups

One hundred nineteen patients included in the present study were investigated and analysed in three study groups : (i) non-smoker males (54); (ii) smoker males (24); and (iii) females (41). Statistical analysis of the data did not show any significant difference between non-smokers and smokers (Table 2.4, 2.8). Therefore, even though tabulated separately for sake of elaboration, their results will be described together. The data on females will also be described along side, to enable the reader make instant comparison. It may be noted that the

first patient in the present study was investigated 128 days after the gas exposure, as it had taken that long to procure the required equipment, install it, standardize techniques, and train personnel. Similarly, the last patient of the study was investigated 1896 days after the gas exposure.

Clinical Profile

Table 2.2 Respiratory Symptoms, Physical Examination and Chest Radiographic Findings in 111 of 119 Patients included in the Study

Reduced work capacity	100	Normal	20.0
Dyspnoea	96	Linear opacities	36.4
Cough	80	Reticulonodular	29.5
Expectoration	70	Reticular	29.5
Pain chest	66	Honey combing	15.9
Physical Findings		Hyperinflation	20.5
Nil	54	Streaky opacities	9.1
Crackles+rhonchi	28	Shrinkage lung	4.5
Rhonchi	16	Raised diaphragm	4.5
Crackles	9	Blocked C-P angle	2.5

It can be seen from Table 2.2 that all patients at the time of study were symptomatic – the most prominent being inability to work, i.e., pulmonary disability on account of dyspnoea/breathlessness. Furthermore, 80% of the chest radiographs showed abnormalities.

Comparison with Acute Phase Observations

Table 2.3 Serial Studies of Lung Function in a Group of Patients

Parameter	n	Predicted Normal	Days After Exposure		
			Study 1 26±10	Study 2 207±45	% change/ p value
FVC (ml)	10	3280±744	1543±782	2447±895	58.6**
FEV1 (ml)	10	2634±416	867±384	1346±456	55.2**
FEV1 (%FVC)	10	80±5	56±17	55±14	p>0.05
FEF25-75% (L/min)	10	185±27	40±23	46±48	3.0
PaO2 (mmHg)	8	80±5	74.7±8.4	74.3±5.7	p>0.05
PaCO2 (mmHg)	8	40±2	33.8±2.8	39.0±1.5	17.8**
pHa	8	7.40±0.02	7.423±0.02	7.387±0.02	** ** p<0.01

Ten patients included in S1 had also been studied in the acute phase of their illness and the results are compared in Table 2.3. It can be seen that they had airflow obstructive-cum-restrictive disorder, and that after apparent recovery their lung function (FVC and FEV_1) had considerably improved, although no change was seen in FEV_1/FVC% or FEF_{25-75} values. It is interesting that in the acute phase the mean PaO_2 was close to normal and was maintained in the follow-up study. $PaCO_2$ which was lower than normal, and pH which was higher initially, were corrected towards normal, meaning that in the acute phase the patients hyperventilated which is typical of pulmonary oedema or pneumonia, as also of anxiety state.

Comparative Analysis of Data of the Three Study Groups

Baseline Characteristics

The data are presented in Tables 2.4 to 2.6. An important finding was that nearly 50% of the patients both males and females judged by their body mass index (BMI) showed evidence of malnutrition (Table 2.6). This is understandable as most of them belonged to lower socio-

economic strata and also had undergone stress associated with the gas disaster. The implication, however, is that protein malnutrition might impair the respiratory muscle strength and therefore the ventilatory capacity.

Table 2.4 Baseline Characteristics of Study Groups : Non-Smoker and Smoker Males Severely Exposed to MIC/Toxic Gas

Parameter	Non-smoker Males		Smoker Males		P
	n	Mean ±SD (Min-Max)	n	Mean ±SD (Min-Max)	>0.05
Age (years)	54	34±14.2 (8-66)	24	39±10.8 (23-60)	>0.05
Height (cm)	54	162±11.7 (123-178)	24	165.8±7.7 (147-178)	>0.05
Weight (kg)	54	52±15 (18-97)	24	51.0±9.2 (39-77)	>0.05
BMI	54	19.6±4.4 (11-32.4)	24	18.5±3.6 (14.4-27.6)	>0.05
Hb (G%)	54	13.1±1.4 (10.2-16.0)	24	13.3±1.2 (11.5-16.0)	>0.05
Days after toxic gas exposure PFT Study S1	54	267±115 (128-700)	24	250±96 (139-587)	>0.05

Table 2.5 Baseline Characteristics of Study Group : Females Severely Exposed to MIC/Toxic Gas

Parameter	n	Mean ±SD	Min - Max
Age (years)	41	32±12	10-55
Height (cm)	41	150.6±7.7	126-166
Weight (kg)	41	46.4±12	22-77
BMI	41	20.2±4.6	14-35
Hb (G%)	41	11.6±1.5	8-14
No. of days between exposure and study			
Study I	41	248±81	153-332
Study II	25	576±66	305-638
Study III	12	1811±77	1581-1896

Table 2.6 Nutritional Status Assessed on the Basis of Body Mass Index (BMI)

Nutritional status	Males (n=78)	Females (n=41)
Normal	35 (44.9)	16 (39.0)
Overweight	6 (7.7)	3 (7.3)
Obese	1 (1.3)	2 (4.9)
Malnourished Mild Moderate Severe	 12 (15.4) 6 (7.7) 18 (23.0)	 11 (26.9) 2 (4.9) 7 (17.0)
Total	78 (100)	41 (100)

Figures in parentheses indicate percent

Static Lung Volumes (SVC, RV, FRC, TLC, RV/TLC%)

Table 2.7 Study Group : Non-Smoker Males Severely Exposed to MIC/Toxic Gas : Pulmonary Function Test and Arterial Blood Gas Values Compared with Predicted Normal Values

Parameter	n	Observed	Predicted	p	Obs./Pred. %
		Mean±SD	Mean±SD		Mean ±SD (Min-Max)
SVC (L)	54	3.14±0.86	3.90±0.88	<0.01	80.42±15.2 (50-130)
RV (L)	53	1.77±0.70	1.45±0.40	<0.01	112.1±32.1 (62-222)
FRC (L)	53	2.82±0.87	2.89±0.86	N.S.	92.3±20.0 (55-154)
TLC (L)	53	4.89±1.20	5.27±1.16	N.S.	92.7±14.5 (60-123)
RV/TLC %	53	35.4±8.0	<35	N.S.	
FVC (L)	54	3.10±0.82	3.86±0.84	<0.0001	80.31±14.3 (49-122)
FEV1 (L)	54	2.29±0.75	3.15±0.70	<0.0001	71.4±19.3 (29-106)
FEF50 (L/Sec)	54	2.93±1.92	4.95±1.33	<0.0001	58.5±35.6 (5-153)

FEF75 (L/Sec)	54	0.91±0.64	2.47±0.6	<0.0001	37.4±24.9 (4-106)
FEF25-75 (L/Sec)	54	2.82±1.40	4.01±0.86	<0.0001	55.5±32.5 (6-120)
PEFR (L/Sec)	54	6.26±2.12	7.37±1.89	<0.05	83.74±23.9 (23-146)
MVV (L/Min)	48	93.3±33.3	102.1±17.7	N.S.	89.7±26.9 (37-148)
DLCO	52	25.7±5.2	28.2±3.4	<0.05	91.1±15.9 (48-119)
KCO	52	6.48±1.20	5.38±0.53	<0.0001	123±17.7 (91-123)
PaO2 (mmHg)	41	83.0±11.5 (Range 62-114)	80-100	N.S.	
PaCO2 (mmHg)	41	38.6±3.0 (Range 29-44)	35-45	N.S.	
pHa (units)	41	7.37±0.02 (Range 7.32-7.43)	7.35-7.45	N.S.	
HCO3 (mmol/L)	41	22.8±1.74 (Range 16.7-27.1)	20-25	N.S.	

Table 2.8 Study Group : Smoker Males Severely Exposed to MIC/Toxic Gas : Pulmonary Function Test and Arterial Blood Gas Values Compared with Predicted Normal Values

Parameter	n	Observed	Predicted	P	Obs./Pred. %	Comparison with non-smokers p value
		Mean±SD	Mean±SD		Mean ±SD (Min-Max)	
SVC (L)	24	3.4±0.74	4.17±0.68	<0.0001	81.75±13.7 (54-113)	>0.05
RV (L)	24	1.98±0.61	1.7±0.25	<0.05	118.6±40.97 (53-232)	>0.05
FRC (L)	24	3.35±0.86	3.51±0.50	N.S.	95.04±21.5 (42-146)	>0.05
TLC (L)	24	5.38±0.88	5.82±0.8	N.S.	93.0±14.12 (69-131)	>0.05
RV/TLC %	24	36.8±8.8	<35	N.S.		>0.05
FVC (L)	24	3.39±0.73	4.17±0.68	<0.0001	81.58±13.6 (55-110)	>0.05
FEV1 (L)	24	2.64±0.77	3.4±0.63	<0.01	77.88±17.76 (36-106)	>0.05
FEF50 (L/Sec)	24	3.11±1.46	5.42±0.57	<0.0001	56.9±25.1 (10-110)	>0.05
FEF75 (L/Sec)	24	1.1±0.74	2.73±0.51	<0.0001	37.25±19.15 (7-82)	>0.05
FEF25-75 (L/Sec)	24	2.42±1.13	4.36±0.55	N.S.	56.6±23.8 (10-94)	>0.05
PEFR (L/Sec)	24	6.43±1.41	8.2±0.95	<0.05	79.21±19.5 (46-127)	>0.05
MVV (L/Min)	17	98.8±29.5	100.8±12.13	N.S.	98.8±24.97 (60-145)	>0.05
DLCO	22	25.15±4.87	28.58±3.4	<0.05		>0.05
KCO	22	5.12±1.08	5.10±0.43	N.S.		<0.05
PaO2 (mmHg)	21	85.1±10.2 (Range 70-102)	80-100	N.S.		
PaCO2 (mmHg)	21	38.4±2.8 (Range 32-43)	35-45	N.S.		
pHa (units)	21	7.39±0.03 (Range 7.37-7.46)	7.35-7.45	N.S.		
HCO3 (mmol/L)	21	23.3±1.54 (Range 20-26.1)	20 to 25	N.S.		

Static Lung Volumes

Males. Both non-smoker and smoker males considered together showed a mild reduction of mean SVC with a corresponding increase in mean RV; both changes being statistically significant (Tables 2.7 and 2.8), physiologically abnormal and clinically relevant. Further analysis of data (Tables 2.10 and 2.11) showed that nearly 50% of the patients had reduced SVC, i.e. less than 80% of predicted. Nearly 65% of the patients had moderate to severe increase in RV, indicating alveolar air trapping due to premature closure of small airways on exhalation, thus retaining a part of SVC in the alveoli. This could lead to hyperinflation of lungs. Mean FRC values were found to be nearly normal, indicating no shift of mid-thoracic position. TLC – the sum total of SVC and RV – showed a marginal reduction which was not found to be statistically significant. This showed alveolo-pleural involvement. Six percent of the cases showed TLC values which were ≥120% of predicted, showing hyperinflation of lungs. Further analysis of stratified data (Table 2.13) showed that 80% of the patients had normal TLC values while 20% showed mild to moderate reduction, but none showed severe reduction.

Table 2.9 Study Group : Females Severely Exposed to MIC/Toxic Gas : Pulmonary Function Test and Arterial Blood Gas Values Compared with Mean Predicted Values

Parameter	n	Observed	Predicted	p	Obs./Pred. %
		Mean±SD	Mean±SD		Mean ±SD (Min-Max)
SVC (L)	41	2.23±0.53	2.97±0.43	<0.001	75.03±14.9 (41-101)
RV (L)	41	1.35±0.43	1.2±0.3	<0.05	117.3±36.8 (53-204)
FRC (L)	41	2.16±0.5	2.56±0.56	<0.01	84.95±24.55 (56-142)
TLC (L)	41	3.60±0.67	4.17±0.66	<0.001	86.8±11.0 (67-104)
RV/TLC %	41	38.27±8.7	<35.0	N.S.	38.27±8.7 (25-65)
FVC (L)	41	2.21±0.53	2.97±0.43	<0.0001	74.71±15.55(41-102)
FEV1 (L)	41	1.77±0.51	2.51±0.35	<0.0001	70.62±18.36(25-103)
FEF50 (L/Sec)	41	2.40±1.15	4.32±0.4	<0.0001	54.98±25.61(7-126)
FEF75 (L/Sec)	41	0.82±0.51	2.54±0.25	<0.0001	32.29±19.54(6-73)
FEF25-75 (L/Sec)	41	1.85±0.93	3.92±0.45	<0.0001	46.9±22.66(6-97)
PEFR (L/Sec)	41	4.36±1.39	5.75±0.54	<0.0001	75.88±22.59(27-114)
MVV (L/Min)	34	64.1±23	81.75±14.4	<0.0001	79.56±29.12(29-150)
DLCO	35	20.49±3.92	24.06±2.22	<0.0001	
KCO	35	6.65±1.04	5.47±2.88	<0.0001	
PaO2 (mmHg)	34	83.4±9.0 Range 64-101	80-100		
PaCO2 (mmHg)	34	37.02±2.93 Range 34-43	35-45		
pHa (units)	34	7.38±0.17 Range 7.33-7.42	7.38-7.44		
HCO3 (mmol/L)	34	22.3±1.95 Range 18.9-26.6	21.0 to 28		

Table 2.10 Study Group : Non-Smoker Males Severely Exposed to MIC/Toxic Gas : Pattern of Pulmonary Function Test and Arterial Blood Gas Values Expressed as Percent Predicted Normal Values

Parameter	n	Percent Mean Predicted			
		<80	81-100	101-120	>120
SVC	54	32 (59.3)	20 (37)	2 (3.7)	0
RV	53	6 (11.3)	16 (30.2)	15 (28.3)	16 (30.2)
FRC	53	16 (30.2)	21 (39.6)	12 (22.6)	4 (7.6)
TLC	53	15 (28.3)	26 (49.1)	9 (17)	3 (5.6)
RV/TLC%	53	11 (20.8)	19 (35.8)	14 (26.4)	9 (17)
FVC	54	33 (61.1)	19 (35.2)	2 (3.7)	0

FEV1	54	37 (68.5)	13 (24.1)	4 (7.4)	0
FEF50	54	36 (66.7)	15 (27.8)	3 (5.5)	0
FEF75	54	51 (94.4)	1 (1.9)	2 (3.7)	0
FEF25-75	54	41 (75.9)	4 (7.4)	9 (16.7)	0
PEFR	54	27 (50)	18 (33.3)	5 (9.3)	4 (7.4)
MVV	48	20 (41.7)	7 (14.6)	13 (27.1)	8 (16.7)
DLCO	52	14 (26.9)	24 (46.2)	14 (26.9)	0
KCO	52	0	9 (17.3)	15 (28.8)	28 (53.9)

Arterial blood gases n = 41; Figures in parentheses indicate percent of total (n).

PO_2 (Predicted normal 80-100 mmHg; Observed : 60-70 mmHg = 6 (14.6); 71-80 mmHg= 13 (31.7); >80 mmgHg = 22 (53.7)

PCO_2 (Predicted normal 35-45 mmHg); Observed : <35 mmHg = 5 (12.2); 36-45 mmHg = 36 (87.8); >45 mmHg = 0

Table 2.11 Study Group : Smoker Males Severely Exposed to MIC/Toxic Gas : Pattern of Pulmonary Function Test and Arterial Blood Gas Values Expressed as Percent Mean Predicted Normal Values

Parameter	n	Percent Mean Predicted			
		<80	81-100	101-120	>120
SVC	24	9 (37.5)	13 (54.2)	2 (8.3)	0
RV	24	2 (8.3)	5 (20.8)	9 (37.5)	8 (33.3)
FRC	24	4 (16.7)	11 (45.8)	7 (29.2)	2 (8.3)
TLC	24	4 (16.7)	14 (58.3)	4 (16.7)	2 (8.3)
RV/TLC%	24	4 (16.7)	6 (25)	7 (29.2)	7 (29.2)
FVC	24	8 (33.3)	14 (58.3)	2 (8.3)	0
FEV1	24	12 (50)	12 (50)	0	0
FEF50	24	20 (83.3)	3 (12.5)	1 (4.2)	0
FEF75	24	23 (95.8)	1 (4.2)	0	0
FEF25-75	24	20 (83.3)	4 (16.7)	0	0
PEFR	24	15 (62.5)	6 (25)	3 (12.5)	0
MVV	17	6 (35.3)	4 (23.5)	3 (17.6)	4 (23.5)
DLCO	22	8 (36.4)	9 (40.9)	4 (18.2)	1 (4.5)
KCO	22	1 (4.5)	7 (31.8)	9 (40.9)	5 (22.7)

Arterial blood gases n = 21; Figures in parentheses indicate percent of total (n)

PO_2, Normal 80-100 mmHg; Observed : <70=0; 71-80 = 7 (33); >80=14 (67)

PCO2, Normal 35-45mmHg; Observed : <35 = 2 (9.5); 36-43 = 19(90.5); >45 = 0

Table 2.12 Study Group : Forty-one Females Severely Exposed to MIC/Toxic Gas : Pattern of Pulmonary Function Test and Arterial Blood Gas Values Expressed as Percent Mean Predicted Normal Values

Parameter	n	Percent of Mean Predicted Values			
		<80	81-100	101-120	>120
SVC	41	26 (63.4)	14 (34.1)	1 (2.4)	0
RV	41	5 (12.2)	13 (31.7)	6 (14.6)	17 (41.5)
FRC	41	18 (43.9)	14 (34.1)	5 (12.2)	4 (9.8)
TLC	41	14 (34.1)	23 (56.1)	4 (9.8)	0
RV/TLC%	41	4 (9.8)	13 (31.7)	9 (22)	15 (35.5)
FVC	41	26 (63.4)	14 (34.1)	1 (2.4)	0
FEV1	41	31 (75.6)	9 (21.9)	1 (2.4)	0
FEF50	41	35 (85.4)	4 (9.8)	2 (4.9)	0
FEF75	41	41 (100)	0	0	0
FEF25-75	41	37 (90.2)	4 (9.8)	0	0
DLCO	35	11 (31.4)	19 (54.3)	5 (14.3)	0
KCO	35	0	4 (11.4)	14 (40)	17 (48.6)

Arterial blood gases n = 32; Figures in parentheses indicate percent of total (n)

PO2 (mmHg) <60 = 0; 60-70 = 3 (8.8); 71-80 = 10 (29.4); >80 = 21 (61.8)

PCO2 (mmHg) 30-35 = 8 (23.5); 36-45 = 26 (76.5); >45 = 0

Table 2.13 Staging of Impairment of Pulmonary Function : Observed Values Expressed as Percent Predicted[10,11]

Parameter	Study group	n	Staging of Impairment (% predicted)			
			0 = Normal ≥80	Mild 66-80	Moderate 50-65	Severe <50
FVC	NSM	54	22 (40.7)	23 (42.6)	7 (13.0)	2 (3.7)
	SM	24	16 (66.7)	5 (20.8)	3 (12.5)	0
	Female	41	15 (36.6)	16 (39.0)	8 (19.5)	2 (4.9)
TLC	NSM	53	40 (75.5)	10 (18.9)	3 (5.7)	0
	SM	24	21 (87.5)	3 (12.5)	0	0
	Female	41	28 (68.3)	13 (31.7)	0	0
FEV1	NSM	54	17 (31.5)	15 (27.8)	14 (25.9)	8 (14.8)
	SM	24	13 (54.2)	5 (20.8)	4 (16.7)	2 (8.3)
	Female	41	10 (24.4) 0 = Normal >70	19 (46.3) Mild 60-70	7 (17.1) Moderate 45-59	5 (12.2) Severe <45
FEV1/FVC%	NSM	54	37 (68.5)	11 (20.4)	5 (9.3)	1 (1.8)
	SM	24	20 (83.3)	2 (8.3)	1 (4.2)	1 (4.2)
	Female	41	36 (87.8) 0 = Normal >65	2 (4.9) Mild 50-65	3 (7.3) Moderate 35-49	0 Severe <35
FEF25-75	NSM	54	17 (31.5)	9 (16.7)	10 (18.5)	18 (33.3)
	SM	24	10 (41.7)	5 (20.8)	5 (20.8)	4 (16.7)
	Female	41	9 (22.0)	10 (24.4)	8 (19.5)	14 (34.1)
FEF50	NSM	54	20 (37.1)	6 (11.1)	10 (18.5)	18 (33.3)
	SM	24	9 (37.5)	7 (29.2)	4 (16.7)	4 (16.7)
	Female	41	12 (29.3)	9 (21.9)	12 (29.3)	8 (19.5)
FEF75	NSM	54	7 (13.0)	9 (16.7)	9 (16.7)	29 (53.7)
	SM	24	2 (8.3)	3 (12.5)	8 (33.3)	11 (45.8)
	Female	41	3 (7.3) 0 = Normal >80	6 (14.6) Mild 61-80	9 (21.9) Moderate 40-60	23 (56.1) Severe <40
DLCO	NSM	52	38 (73.1)	13 (25.0)	1(1.9)	0
	SM	22	14 (63.6)	8 (36.4)	0	0
	Female	35	24 (68.6)	11 (31.4)	0	0

NSM = Non-smoker males; SM = Smoker males
Figures in parentheses indicate percent of total (n)

Females. Tables 2.9, 2.12 and 2.13 show that females, compared with males, showed a relatively greater reduction of SVC, about the same increase of RV; and significant reduction of FRC and TLC. Further analysis of data showed that 68% patients had normal TLC while only 32% showed mild reduction of TLC and none showed moderate or severe reduction (Table 2.13) or hyperinflation. Thus, female patients showed a marginal reduction of overall size of lungs, with downward shift of mid thoracic position.

RV/TLC% showed mild increase in 25.4% and moderate to severe increase in 26.3% of all the patients of three study groups considered together, indicating the degree of increase in residual volume in relation to the total lung capacity (Tables 2.10 to 2.12).

Dynamic Lung Volumes (FVC, FEV_1, FEF_1/FVC%)

The dynamic lung volumes are the most frequently used measurements in clinical practice, because of their high specificity and sensitivity in the diagnosis and management of airflow obstructive, restrictive and combined (obstructive cum restrictive) pulmonary impairment. It

is easy to measure, very reproducible and the test can be performed even by relatively unwell patients. Most important, the test values are relatively effort independent.

FVC. The mean FVC values in all three study groups follow nearly the same distribution as for SVC.

FEV1. Mean FEV1 values in all three study groups showed mild but statistically significant reduction (p=<0.001) i.e. below 80% of predicted normal (Tables 2.7 to 2.9). Further analysis of data showed that nearly 65% of the patients had reduced FEV1 (<80% of predicted), if 80% is considered the cut off point (Tables 2.10 to 2.12). The data have also been analysed according to Comroe and Nadel10 and Murray and Nadel11 (Table 2.13). It can be seen that 33% of patients had normal (>80% of predicted), 33% showed mild reduction (66-80% predicted), 21% showed moderate (50 to 65% predicted) and the remaining 13% showed severe reduction (<50% predicted).

FEV_1/FVC Ratio. FEV_1 expressed as % of FVC showed normal values in nearly 87% patients of the three groups considered together, while 13% patients showed mild, moderate or severe impairment[10-11] (Table 2.13). FVC and FEV_1/FVC% were also used to classify pulmonary function into normal, restrictive, obstructive and combined (restrictive cum obstructive) pulmonary impairment (see Table 2.14). Two cut off points, i.e., 75% and 80% were used i.e. 80% or 75% of predicted normal FVC and of FEV_1/FVC%. Clinically, however, 75% cut off point seemed more appropriate for defining the type of pulmonary impairment (see Table 2.14). Using this criteria it can be seen that in all three study groups together, 42.9% were normal, 20.2% showed evidence of restrictive, 11.8% obstructive, and 25.2% showed evidence of combined (restrictive cum obstructive) pulmonary impairment. This method of assessment is perhaps very convenient for clinical purpose. Ideally, however, total lung capacity and residual volume should also be taken into account for identifying different types of abnormalities.

Table 2.14 Showing Types of Pulmonary Impairment in Non-Smoker (NSM), Smoker Males (SM), and Females : Normal = FVC>80% or 75% Predicted and FEV_1/FVC>80% or 75%

Impairment Type	80% Level				75% Level			
	NSM	SM	F	Total	NSM	SM	F	Total
0=Normal	11(20.4)	7(29.2)	9(22)	27(22.7)	23(42.6)	13(54.2)	15(36.6)	51(42.9)
Restrictive	14(25.9)	5(20.8)	13(31.7)	32(26.9)	7(13.0)	2(8.3)	15(36.6)	24(20.2)
Obstructive	10(18.5)	9(37.5)	6(14.6)	25(21.0)	4(7.4)	5(20.8)	5(12.2)	14(11.8)
Combined	19(35.2)	3(12.5)	13(31.7)	35(29.4)	20(37.0)	4(16.7)	6(14.6)	30(25.2)
Total	54(100)	24(100%)	41(100)	119(100%)	54(100)	24(100%)	41(100)	119(100%)

Figures in parentheses indicate percent of total
Restrictive = FVC<80% or 75%, FEV_1/FVC% >80% or 75%
Obstructive = FVC>80% or 75%, FEV_1/FVC% <80% or 75%
Obstructive cum restrictive (combined) = FVC <80% or 75%, FEV_1/FVC% <80% or 75%

Forced expiratory flow rates (PEFR, $FEF_{50, 75}$, and $_{25-75\%}$)

The determinants of forced expiratory flow rates are the lung volume, size of airway lumen, elastic properties of lungs and to some extent the respiratory muscle force. The flow rates are therefore higher near the peak inspiratory position (PEFR) and lowest close to RV (FEV_{75}) – the point at which the small airways actually close. Technically, PEFR and FEF_{75} measurement are more effort dependent than FEF_{25-75} and FEF_{50}. These tests are useful in the diagnosis of airflow obstructive disorders like asthma/COPD and to some extent differentiating between central and small/peripheral airway obstruction.

PEFR values, considered for all the study groups together showed only mild impairment (Tables 2.7 to 2.9). Further analysis of data showed that 60 to 75% cases had low values, i.e. <80% of predicted (Tables 2.10 to 2.12). The mean values of FEF_{50}, FEF_{25-75} and FEF_{75} showed moderate to severe reduction in equal measure in all three study groups (Tables 2.7 to 2.9). In 60-90% cases the observed values were found to be lower than the 80% predicted normal (Tables 2.10 to 2.12). The expiratory flow rate data were further analysed according to Comroe, Nadel and Murray[10,11] (Table 2.13). It can be seen that FEF_{75} were the worst affected in all study groups in, that only 10% had normal values, 15% showed mild reduction, 22% showed moderate reduction, while 53% had severe reduction. It may be concluded that small/peripheral airways less than 2 mm dia. were the worst affected in almost all severely exposed patients. This also explains the increased RV and alveolar air trapping in a large number of cases.

MVV measurement is a test for integrated function of lung elasticity, size of airway lumen, and respiratory muscle force. The values are dependent on effort and motivation. In males, there was no significant difference between the mean observed and the predicted values (Tables 2.7, 2.8), while in females the MVV values showed a mild but statistically significant reduction (Table 2.9). Further analysis of data showed that MVV was mildly reduced in 35 to 50% cases, while in the remaining the test values were within the normal range.

Bronchoreversibility Test

Table 2.15 Study Group : Non-Smoker Males Severely Exposed to MIC/Toxic Gas :

Parameter	N	Percent Change After Inhaled Salbutamol						p
		->10	-1 to 10	0 to 5	6 to 10	11 – 15	>15	
FVC	40	0	11 (27.5)	23 (57.5)	5 (12.5)	1 (2.5)	0	<0.01
FEV1	40	0	4 (10)	22 (55)	8 (20)	2 (5)	4 (10)	<0.001
FEF50	40	4 (10)	6 (15)	5 (12.5)	1 (2.5)	5 (12.5)	19 (47.5)	<0.01
FEF75	40	7 (17.5)	5 (12.5)	4 (10)	7 (17.5)	1 (2.5)	16 (40)	<0.05
FEF25-75	40	6 (15)	7 (17.5)	3 (7.5)	4 (10)	4 (10)	16 (40)	<0.01
PEFR	40	5 (12.5)	6 (15)	5 (12.5)	4 (10)	4 (10)	16 (40)	<0.05
MVV	34	1 (2.9)	3 (8.8)	12 (35.3)	4 (11.8)	0	14 (41.2)	<0.001

Figures in parentheses indicate percent of total (n)
p = paired sample t test for pre and post bronchodilator

Table 2.16 Study Group : Smoker Males Severely Exposed to MIC/Toxic Gas : Response to Single Inhalation of 400 μg Salbutamol Aerosol

Parameter	n	Percent Change After Inhaled Salbutamol						p
		->10	-1 to 10	0 to 5	6 to 10	11 – 15	>15	
FVC	18	0	7 (39)	5 (28)	4 (22)	2 (11)	0	<0.05
FEV1	18	0	5 (28)	7 (39)	4 (22)	1 (5.5)	1 (5.5)	<0.05
FEF50	18	3 (16.7)	2 (11)	0	3 (16.7)	3 (16.7)	7 (39)	N.S.
FEF75	18	7 (39)	1 (5.5)	2 (11)	2 (11)	1 (5.5)	5 (28)	N.S.
FEF25-75	18	5 (28)	0	3 (16.7)	1 (5.5)	3 (16.7)	6 (33.3)	N.S.
PEFR	18	4 (22.2)	6 (33.3)	0	1 (5.5)	0	7 (39)	N.S.
MVV	18	0	0	3 (30)	1 (10)	1 (10)	5 (50)	<0.01

Figures in parentheses indicate percent of total (n)
p = paired sample t test for pre and post bronchodilator

Table 2.17 Study Group : Females Severely Exposed to MIC/Toxic Gas : Response to Single Inhalation of 400 μg Salbutamol Aerosol

Parameter	n	Percent Change After Inhaled Salbutamol						p
		->10	-1 to 10	0 to 5	6 to 10	11 – 15	>15	
FVC	36	0	3 (8.3)	29 (80.6)	2 (5.6)	1 (2.8)	1 (2.8)	<0.01
FEV1	36	0	7 (19.4)	18 (50.0)	7 (19.4)	3 (8.3)	1 (2.8)	<0.05
FEF50	36	2 (5.6)	4 (11.1)	9 (25.0)	5 (13.9)	4 (11.1)	12 (33.3)	<0.01
FEF75	36	8 (22.2)	4 (11.1)	6 (16.7)	5 (13.9)	0	13 (36.1)	>0.05
FEF25-75	36	1(2.8)	1 (2.8)	11 (30.6)	4 (11.1)	4 (11.1)	15 (41.7)	<0.05
PEFR	36	3 (8.3)	12 (33.3)	3 (8.3)	7 (19.4)	5 (13.9)	6 (16.7)	>0.05
MVV	34	1 (2.9)	2 (5.9)	16 (47.1)	2 (5.9)	5 (14.7)	8 (23.5)	<0.05

Figures in parentheses indicate percent of total (n)
p = paired sample t test for pre and post bronchodilator

The effect of a single inhalation of 400 μg salbutamol aerosol could be tested in 94 of 119 patients included in the study (see Tables 2.15 to 2.17). The main purpose of this test was to find out whether the airflow obstruction in a given case was significantly reversible, meaning that such patients would be likely to benefit from treatment with inhaled bronchodilators. Significant reversibility means an increase of more than 15%, subject to minimum 200 ml FEV_1, which may also be accompanied by increase in expiratory flow rates, and MVV after inhalation of 400 μg salbutamol aerosol. This magnitude of response is considered diagnostic of asthma. It should also be noted that in normal persons as well as in COPD, FEV_1 response remains less than 15%, which is considered insignificant. Bronchoreversibility test results are presented in Tables 2.15 to 2.17. It can be seen that increase in FEV_1, expiratory flow rates and MVV is statistically significant, but asthmatic response i.e. ≥15% increase in FEV1 was seen in 6 of the 94 patients tested. In other cases, some increase in FEV_1 and or expiratory flow rates may mean airway hyper-responsiveness in response to toxic gas inhalation causing airway injury. It may also mean that the patients might benefit from inhalation of bronchodilators.

Lung Transfer Factor (DLCO) and KCO (Single Breath CO Diffusion Capacity of Lungs)

All the three study groups showed mild but statistically significant reduction of mean DLCO (Tables 2.7 to 2.9). Stratification of data reveals that the DLCO values are <80% of predicted normal in 30(40.5%) of 74 males and 11(36.7%) of 30 female patients (Tables 2.10 to 2.12). The data have been further analysed[10-11] (Table 2.13). It can be seen that out of the total 109 cases 70% showed normal values, 29% showed mild reduction and 1% showed moderate but none showed severe reduction of DLCO. Mean KCO (DLCO per unit of lung volume) values showed no significant change from predicted normal values in non-smoker males, but a mild significant increase in smoker males and females. DLCO actually measures the gas exchange through alveolo-capillary membrane, and is not synonymous with arterial blood gases.

Arterial Blood PO_2, PCO_2, PH and HCO_3

For all study groups together, 96 patients arterial blood was tested which showed no significant difference in the mean PO_2, PCO_2, pH and HCO_3 from the normal range of their respective predicted values (Tables 2.7 to 2.9). Further analysis of stratified data showed no case of type 1 or type 2 respiratory failure, only 6% cases showed marginal reduction of PO_2. The arterial blood gases, pH and HCO_3, actually represent the efficiency of the integrated function of ventilation, perfusion (V/Q ratio), and diffusion.

Follow-up Studies (S2 and S3)

In all three study groups, after the initial study (S1) first follow-up study (S2) was carried out about six months to one year after S1, and a second follow-up study (S2) was carried out 4-5 years after the date of gas exposure, i.e., $2^{nd}/3^{rd}$ December, 1984. All patients of S1 were contacted by home visits and requested to come to the Respiratory Laboratory but only the following number of them responded positively : (i) Non-smoker males – out of total of 54 in S1, 38 responded for S2 and only 22 patients responded for S3; (ii) smoker males – out of total of 24 (S1), 21 responded for S2 and 12 patients responded for S3; (iii) females – out of total of 41 (S1), 25 responded for S2 and 12 patients responded for S3. It was felt by the home visitor that patients who were feeling better over the years were reluctant to report for follow-up studies. Also, several of them had moved out of their earlier residence and thus were not traceable. The methodology used in performing the tests was exactly the same as in the initial study, i.e., S1.

Analysis of Data

All test values for each of the parameter for each of the patients in S2 and S3 were tabulated as difference from the S1 values, and the data were statistically analysed as in S1. The results are presented in Tables 2.18 to 2.22. The lapse of time between S1 and S2, S1 and S3 in each of the study group is shown as number of days after the toxic gas exposure i.e., $2^{nd}/3^{rd}$ December, 1984.

Table 2.18 Study Group. Non-Smoker Males Severely Exposed to MIC/Toxic Gas : Change in Pulmonary Function Test and Arterial Blood Gas Values in the Follow-up Studies II and III Compared with Study I

Parameter	N	Study II (S2) Minus Study I (S1)	N	Study III (S3) minus Study I (S1)
		Mean±SD (Min/Max)		Mean ±SD (Min/Max)
Days after gas exposure	38	600±170 minus 256±107	22	1757±102 minus 256±107
SVC (ml)	38	47±272 (-550 to 870)	22	-42±225 (-550 to 410)
RV (ml)	37	-199±260 (-750 to 250)	22	-134±275 (-840 to 330)
FRC (ml)	37	-174±293 (-700 to 450)	22	-208±398 (-910 to 650)
TLC (ml)	37	-156±332 (-1210 to 500)	22	-171±331 (-650 to 510)
FVC (ml)	38	62±277 (-620 to 790)	22	-68±252 (-480 to 430)
FEV1 (ml)	38	-7±208 (-590 to 430)	22	-8±187 (-380 to 360)
FEF50 (L/Sec)	38	-0.17±0.85 (-2.01 to 2.35)	22	-0.86±1.2 (-5 to 0)
FEF75 (L/Sec)	38	-0.03±0.49 (-1.43 to 1.49)	22	-0.24±0.49 (-1 to 1)
FEF25-75 (L/Sec)	38	-0.14±0.69 (-2.1 to 1.7)	22	-0.45±0.74 (-3 to 1)
PEFR (L/Sec)	38	-0.26±1.39 (-5.13 to 2.31)	21	-0.62±1.52 (-3 to 4)
MVV (L/Min)	33	-1.4±16.0 (-34 to 25)	18	-6.5±18.6 (-49 to 37)
DLCO	36	-0.7±3.0 (-6 to 9)	19	-0.45±3.5 (-6 to 5)
KCO	36	-0.43±1.93 (-11 to 2)	19	-0.4±2.1 (-1 to 9)
PaO2 (mmHg)	28	-0.25±6.1 (-13 to 10)	-	-
PaCO2 (mmHg)	28	0.31±2.6 (-5 to 7)	-	-

Table 2.19 Study Group. Smoker Males Severely Exposed to MIC/Toxic Gas : Differences in Pulmonary Function Test and Arterial Blood Gas Values in Follow-up Study II and Study III Compared with Study I

Parameter	N	Study II Minus Study I	n	Study III Minus Study I
		Mean±SD (Min/Max)		Mean ±SD (Min/Max)
No. days post-exp.	21	725±382 minus 245±98	12	1859±168 minus 245±98
SVC (ml)	21	61±268 (-550 to 560)	12	-21±282 (-550 to 470)
RV (ml)	21	-166±316 (-640 to 620)	12	-119±169 (-440 to 110)
FRC (ml)	21	-196±420 (-1480 to 550)	12	-228±325 (-910 to 160)
TLC (ml)	21	-58±373 (-610 t0 670)	12	-93±386 (-650 to 600)
FVC (ml)	21	47±283 (-390 to 670)	12	-43±222 (-380 to 340)
FEV1 (ml)	21	-66±216 (-370 to 430)	12	-143±205 (-470 to 360)
FEF50 (L/Sec)	21	-0.31±0.91 (-2.03 to 2.35)	12	-0.37±0.67 (-1 to 2)
FEF75 (L/Sec)	21	-0.24±0.66 (-2.60 to 0.55)	12	-0.13±0.40 (-1 to 1)
FEF25-75 (L/Sec)	21	0.27±0.66 (-1.40 to 1.74)	12	-0.20±0.39 (-1 to 0.0)
PEFR (L/Sec)	21	0.27±1.35 (-1.55 to 3.86)	12	-0.72±0.98 (-3 to 1)
MVV (L/Min)	17	2.53±15.7 (-23 to 29)	11	-1.00±19.9 (-32.0 to 41)
DLCO	19	-0.53±2.26 (-5 to 4)	10	-0.25±2.29 (-4 to 4)
KCO	19	-0.43±0.47 (-2 to 0)	10	-0.22±0.55 (-1 to 1)
PaO2 (mmHg)	18	-1.95±5.15 (-13 to 4)		-
PaCO2 (mmHg)	18	0.79±3.83 (-7 to 9)		-

Table 2.20 Study Group. Forty-one Females Severely Exposed to MIC/Toxic Gas : Differences in Pulmonary Function Test and Arterial Blood Gas Values in Follow-up Study II and Study III Compared with Study I

Parameter	N	Study II Minus Study I	n	Study III – Study I
		Mean±SD (Min/Max)		Mean ±SD (Min/Max)
No. days post-exp.	25	576±66 minus 216±45	12	1811±77 minus 216±45
SVC (ml)	25	109±225 (-190 to 810)	12	30±230 (-390 to 350)
RV (ml)	23	-152±189 (-700 to 60)	12	23±221 (-300 to 540)
FRC (ml)	23	-143±221 (-680 to 140)	12	-156±267 (-640 to 320)
TLC (ml)	23	-38±195 (-330 t0 290)	12	25±203 (-220 to 380)
FVC (ml)	25	150±272 (-200 to 1020)	12	174±377 (-320 to 1010)
FEV1 (ml)	25	68±157 (-270 to 530)	12	3±208 (-300 to 370)
FEF50 (L/Sec)	25	-0.13±0.48 (-0.72 to 1.30)	12	-0.24±0.61 (-1.34 to 0.70)
FEF75 (L/Sec)	25	-0.11±0.28 (-1.0 to 0.59)	12	-0.42±0.72 (-1.5 to 0.42)
FEF25-75 (L/Sec)	25	-0.06±0.44 (-1.45 to 1.24)	12	-0.28±0.51 (-1.15 to 0.7)
PEFR (L/Sec)	25	0.31±0.87 (-1 to 3)	12	0.12±1.59 (-2.53 to 2.59)
MVV (L/Min)	25	5.70±13.2 (-16 to 42)	12	-2.55±15.3 (-25 to 29)
DLCO	18	-0.95±2.86 (-7 to 4.5)	9	-0.83±5.24 (-6.48 to 11.0)
KCO	18	-0.18±0.96 (-2.33 to 1.2)	9	-0.05±1.53 (-2.04 to 3.21)
PaO2 (mmHg)	19	0.63±7.9 (-18 to 17)	-	-
PaCO2 (mmHg)	19	1.36±1.86 (-1.9 to 4.8)	-	-

Static lung volumes. It can be seen that in both non-smoker and smoker males the 1st follow-up study i.e., S2 showed a very small increase in mean SVC, with a significant reduction of RV, FRC and TLC. Five years after the exposure these test values showed a little reduction from S2 values. It can be seen that the difference between S2-S1 and S3-S1 was small and on either side of S1 values that it was not statistically significant. The static lung volumes in females followed the same general pattern.

Dynamic lung volumes (FVC, FEV_1). Mean FVC and FEV1 values followed almost the same trend as static lung volumes in males, but in females the marginal improvement in S2 was maintained in S3.

Expiratory flow rates. In non-smoker males the reduced expiratory flow rates in S1 and S2 showed a further reduction in S3, while in smoker males and females, there was no further reduction in S3.

DLCO, KCO and arterial blood gases. There were no significant changes from initial study (S1). Fewer and fewer patients agreed to get arterial blood examined in S2 and S3 (almost none). It can be appreciated from the above data that the different test values had varied on either side i.e., reduction/increase from the S1 test values. In order to understand the range of variation, the entire data for the three study groups were stratified and further analysed. The results are presented in Tables 2.21 and 2.22. It is clear from these tables that the variations in all test values in the follow-up studies S2 and S3 were uniformly distributed around the test values of the initial study S1 and would not be statistically significant.

Table 2.21 Percent Changes in Pulmonary Function Test Parameters in Study II (S2) Compared with Study I (S1) in the Three Study Groups : Non-Smoker Males (NSM), Smoker Males (SM) and Females

Parameter	Study group	n	Study II (S2) – Study I (S1) : % Total					
			-<10	-10 to 15	->15	+<10	10-15	>15
SVC	SM	21	19.0	9.5	0	57.2	4.8	9.5
	NSM	38	28.9	7.9	0	52.6	5.3	5.3
	Female	25	24.0	0	0	44.0	16.0	16.0
RV	SM	21	14.3	14.3	42.9	9.5	4.8	14.3
	NSM	37	24.3	16.2	32.4	18.9	2.7	5.4
	Female	23	56.5	13.0	21.7	8.8	0	0
FRC	SM	21	52.4	9.5	9.5	14.3	0	14.3
	NSM	37	45.9	10.8	16.2	18.9	5.4	2.7
	Female	23	34.8	8.8	21.7	34.8	0	0
TLC	SM	21	57.2	0	0	33.3	9.5	0
	NSM	37	59.5	5.4	2.7	29.7	0	2.7
	Female	23	52.2	0	0	43.5	4.3	0
FVC	SM	21	23.8	9.5	0	57.2	0	9.5
	NSM	38	31.6	5.3	0	50.0	5.3	7.9
	Female	25	24.0	0	0	44.0	16.0	16.0
FEV1	SM	21	42.9	14.3	4.8	28.6	0	9.5
	NSM	38	42.1	7.9	7.9	26.3	10.5	5.3
	Female	25	32.0	0	4.0	44.0	0	20.0
FEF50	SM	21	14.3	14.3	47.6	9.5	4.8	9.5
	NSM	38	15.2	5.3	39.5	13.2	5.3	21.5
	Female	25	24.0	8.0	28.0	12.0	8.0	20.0
FEF75	SM	21	14.3	4.8	47.6	0	9.5	23.8
	NSM	38	13.2	5.3	44.7	10.5	0	26.3
	Female	25	20.0	0	52.0	8.0	8.0	12.0
FEF25-75	SM	21	14.3	19.0	42.9	9.5	0	14.3
	NSM	38	18.4	5.3	36.8	26.3	2.6	10.5
	Female	25	32.0	12.0	16.0	20.0	4.0	16.0
PEFR	SM	21	23.8	4.8	19.0	19.0	0	33.3
	NSM	38	31.6	7.9	23.7	15.8	2.6	18.4
	Female	25	16.0	12.0	4.0	24.0	12.0	32.0

MVV	SM	17	11.8	11.8	11.8	29.4	0	35.3
	NSM	33	18.2	6.1	21.2	24.2	9.1	21.2
	Female	23	13.0	0	17.4	26.1	4.3	39.1
DLCO	SM	19	36.8	10.5	5.3	31.6	10.5	5.3
	NSM	36	25.0	19.4	11.1	36.1	2.8	5.6
	Female	18	44.4	0	16.7	27.8	5.5	5.5
KCO	SM	19	52.6	15.8	15.8	10.5	5.3	0
	NSM	36	19.4	25.0	11.1	30.6	5.6	8.3
	Female	18	38.9	11.1	5.5	16.7	5.5	22.2

NSM = Non-smoker males; SM = Smoker males

Table 2.22 Percent Changes in Pulmonary Function Test Parameters in Study III (S3) Compared with Study I (S1) in the Three Study Groups : Non-Smoker Males (NSM), Smoker Males (SM) and Females

Parameter	Study group	n	Study III (S3) – Study I (S1) : % Total					
			-<10	-10 to 15	->15	+<10	10-15	>15
SVC	SM	12	41.7	16.7	0	25.0	8.3	8.3
	NSM	22	36.4	13.6	4.5	36.4	9.1	0
	Female	12	41.7	0	8.3	25.0	8.3	16.7
RV	SM	12	66.7	8.3	8.3	16.7	0	0
	NSM	22	31.8	13.6	22.7	22.7	0	9.1
	Female	12	41.7	8.3	0	33.3	0	16.7
FRC	SM	12	50.0	8.3	16.7	16.7	8.3	0
	NSM	22	36.4	13.6	22.7	13.6	4.5	9.1
	Female	12	25.0	33.3	16.7	16.7	8.3	0
TLC	SM	12	58.3	8.3	0	16.7	16.7	0
	NSM	22	59.1	13.6	0	22.7	4.5	0
	Female	12	41.7	0	0	50	8.3	0
FVC	SM	12	41.7	16.7	0	33.3	0	8.3
	NSM	22	13.6	9.1	9.1	59.1	9.1	0
	Female	12	41.7	0	8.3	25.0	8.3	16.7
FEV1	SM	12	41.7	16.7	16.7	16.7	8.3	0
	NSM	22	40.9	18.2	4.5	31.8	4.5	0
	Female	12	33.3	16.7	0	25.0	0	25.0
FEF50	SM	12	8.3	25.0	58.3	0	0	8.3
	NSM	22	18.2	4.5	63.6	13.6	0	0
	Female	12	8.3	0	41.7	16.7	0	33.3
FEF75	SM	12	16.7	16.7	41.7	0	8.3	16.7
	NSM	22	4.5	9.1	63.6	4.5	4.5	13.5
	Female	12	8.3	0	58.4	0	0	33.3
FEF25-75	SM	12	8.3	16.7	50.0	16.7	0	8.3
	NSM	22	4.5	13.7	59.0	9.1	0	13.7
	Female	12	16.7	16.7	50.0	0	0	16.7
PEFR	SM	12	16.7	8.3	50.0	16.7	8.3	0
	NSM	22	9.1	9.1	45.5	18.2	9.1	9.1
	Female	12	8.3	8.3	16.7	16.7	8.3	41.7
MVV	SM	11	18.2	9.1	27.3	18.2	9.1	18.2
	NSM	18	11.1	16.7	22.2	38.9	5.6	5.6
	Female	11	9.1	0	36.4	27.2	9.1	18.2
DLCO	SM	10	50	10.0	0	30.0	0	10.0
	NSM	19	26.3	10.5	15.8	21.1	5.3	21.1
	Female	9	22.2	0	33.3	33.3	0	11.1
KCO	SM	10	40.0	10.0	10.0	30.0	10.0	0
	NSM	19	26.2	15.8	10.5	31.6	10.5	5.4
	Female	9	33.3	11.1	22.2	11.1	0	22.2

NSM = Non-smoker males; SM = Smoker males

Cardio-Pulmonary Exercise Test (CPET)

Fifty-three of the 78 male patients (non-smoker = 36, smoker = 17) performed CPET in the initial study S1. In the follow-up study S2 only 21 patients (non-smoker = 12, smoker = 9) could be tested. The results are presented in Tables 2.23 to 2.26.

Table 2.23 Symptoms at the Time of Stopping Exercise in Non-Smoker and Smoker Males Undergoing Symptom Limited Incremental Work Load Cycle Ergometry : Total No. of Tests in Initial Study i.e. S1 = 53, Follow-up Study i.e. S2=27

Sl.No.	Symptom	n	% Total
1.	Mild breathlessness	10	12.5
2.	Moderate breathlessness	31	38.8
3.	Severe breathlessness	30	38.0
4.	Pain chest	13	16.3
5.	Fatigue/ache/heaviness/pain calf mucles, knee joints and feet	56	70
6.	Stiffness/fatigue/pain thighs	22	27.5
7.	Giddiness	10	12.5
8.	Black-out	3	3.8
9.	"Ghabrahat"	2	2.5
10.	Lack of motivation	3	3.8
11.	Headache	3	3.8
12.	Palpitation	3	3.8

Table 2.24 Cardio-pulmonary Response to Initial CPET (S1) Incremental (Ramp Pattern) Work Load in Males Severely Exposed to MIC/Toxic Gas Mean ±SD (Max – Min)

Parameter	Study group	N	Predicted	Observed	Observed/Predicted %	NS vs S p
Baseline FEV1 (L)	NS	36	3.41±0.40 (4.1-2.5)	*2.51±0.47 (3.92-1.12)	73.7±17.8 (106-42)	
	S	17	3.58±0.53 (4.5-2.6)	*2.75±0.77 (3.85-1.12)	76.7±17.7 (106-36)	>0.05
	Total	53	3.46±0.45 (4.5-2.5)	*2.59±0.69 (3.92-1.12)	74.7±17.7 (106-36)	
VE (L)	NS	36	106.1±12.7 (135.2-78)	*43.8±7.9 (61.3-26.6)	41.7±8.2 (59-23)	>0.05
	S	17	103.9±13.1 (133.6-78)	*40.0±7.7 (50.2-23)	38.6±6.8 (48-26)	
	Total	53	105.4±12.8 (135.2-78)	*42.6±8.0 (61.3-23)	40.7±7.9 (59-23)	>0.05
VO2 (L)	NS	36	2.28±0.45 (4.0-1.6)	*1.31±0.31 (1.9-0.7)	58.39±11.48 (77-33)	
	S	17	1.93±0.32 (2.4-1.2)	*1.17±0.27 (1.6-0.6)	57.6±16.07 (75-6)	>0.05
	Total	53	2.17±0.44 (4.0-1.2)	*1.26±0.30 (1.9-0.6)	58.13±13.0 (77-6)	
HR	NS	36	188±7.4 (174-201)	*138±20.3 (173-100)	72.59±9.61 (91-54)	>0.05
	S	17	186±6.4 (171-194)	*132±15.2 (163-109)	70.77±7.21 (85-61)	
	Total	53	187±7.1 (201-171)	*136±18.9 (173-100)	72.01±8.88 (91-54)	

S = Smoker; NS = Non-smoker; VE = Ventilation per min; VO2 = Oxygen uptake/min; HR = Heart rate per min

*$p<0.001$; difference between predicted and observed

Physical Characteristics of Study Sample NS VS S

	NS n = 36	S n = 17	NS vs S (p)
Age	33.6±9.1	35.6±8.3	>0.05
Height (cm)	165.1±7.3	167.1±6.9	>0.05
Weight (kg)	56.1±9.5	50.5±8.6	>0.05
Hb (G%)	13.3±1.5	13±1.3	>0.05
BMI	20.5±1.9	18.22±2.1	>0.05

Table 2.25 CPET: Cardio-Pulmonary Response to Incremental Work Load

Parameter	**Study Groups**						p NS vs S
	n	**Non-smoker**	**n**	**Smoker**	**n**	Total	
Indirect MBC	36	75.3±19.4(118-34)	17	82.5±23.0(115-33)	53	77.6±20.7(118-33)	>0.05
Work (Watts)	36	92.8±24.7(130-37)	17	83.7±29.3(116-29)	53	89.9±26.3(130-29)	>0.05
RR (per min)	36	35.8±11.1(70-24)	17	31.9±6.9(49-24)	53	34.6±10(70-24)	>0.05
VT (L)	36	1.24±0.36(2.1-0.61)	17	1.25±0.28(1.76-0.78)	53	1.24±0.33(2.1-0.61)	>0.05
R.Q.	36	1.01±0.08(1.22-0.87)	17	1.04±0.09(1.27-0.90)	53	1.02±0.08(1.27-0.87)	>0.05
VE/Indirect MBC%	36	61.4±17.9(118-35)	17	52.2±20.5(113-32)	53	58.4±19.1(118-53)	>0.05
VEq O2	36	34.1±7.8(59.3-22.8)	17	35.0±6.3(52-25.9)	53	34.4±7.3(59.3-22.8)	>0.05
VO2/kg	36	23.21±6.7(35.7-11.1)	17	23.52±5.1(30.0-12.2)	53	23.3±6.2(35.7-11.1)	>0.05
O2 Pulse	36	9.20±1.7(12.7-6.1)	17	8.7±2.2(12.5-4.0)	53	9.0±1.9(12.7-4.0)	>0.05
K Cal	36	5.6±1.4(8.5-2.9)	17	5.1±1.2(6.8-2.3)	53	5.4±1.3(8.5-2.3)	>0.05

Figures in parentheses indicate maximum to minimum values

Table 2.26 Follow-up CPET (S2) : Difference in Cardio-Pulmonary Responses – Compared with Initial Study (S1)

Parameter	**Non-smoker n = 18 S2 – S1 Mean ±SD (Max/Min)**	**Smoker n = 9 S2 – S2 Mean±SD (Max/Min)**	**p NS vs S**
No. days interval S2 – S1	337±91 (461-185)	344±77 (257-478)	>0.05
FEV1 (ml)	*18±161 640, (-260)	*60±267 430, (-370)	>0.05
VO2 (L)	*-0.05±0.16 0.2, (-0.4)	*0.06±0.24 0.2 (-0.5)	>0.05
VE (L)	*-0.906±5.92 9.0, (-12.4)	*-0.87±7.0 9.7, (-13.8)	>0.05
HR (per min)	*-1.2±10.5 15, (-26)	*-2.4±14.0 15, (-25)	>0.05
R.Q.	*0.03±0.09 0.22, (-0.11)	*-0.06±0.1 0.14 (-0.25)	>0.05

*p>0.05 – not significant

Table 2.23 shows the range of symptoms which were responsible singly or collectively for limiting the exercise test. It may be noted that severe breathlessness was responsible only in 38% cases; the more common limiting factors being mild and moderate breathlessness, fatigue, discomfort in thighs, calf muscles, knee joints and feet. Most patients complained of more than one symptom.

Baseline FEV_1. FEV_1 is one of the main determinants of exercise capacity. Out of the 53 patients who performed exercise test 20 (37.7%) had normal FEV_1, 16 (30.2%) had mild, 12 (22.6%) moderate and 5 (9.4%) had severe impairment of FEV_1 values, according to classification given in Table 2.13. CPET data are presented in Tables 2.24 and 2.25. It can be noted from Table 2.24 that the differences between the predicted and observed values of FEV_1, ventilation, O_2 uptake and heart rate were highly significant ($p<0.001$), while there was no significant difference between smokers and non-smokers. It can also be noted that the oxygen uptake at the break-point of exercise test remained far below the predicted capacity. But more importantly, at the break-point the patients were still left with lot of ventilatory as well as the cardiovascular reserve capacity. This means that the exercise capacity was not limited only due to respiratory or cardiovascular systems. Table 2.25 presents the various CPET parameters, which do not show any gross abnormality. In particular, the Veq values did not show abnormally high ventilation per litre of oxygen uptake; as also the VO_2/kg, R.Q. and O_2 pulse values showed normal utilization of oxygen at tissue level. It may also be noted that at the break-point work rates achieved were proportionate to other responses. Rather low VE/indirect MBC values also supported the finding that at break-point of exercise maximum breathing capacity had not been utilized. The CEPT results suggested that unexplained exertional dyspnoea and reduced work capacity could be due to a combination of : reduced FEV_1, increased RV, psychogenic factors for poor effort, physiological deconditioning, high level of anxiety, protein malnutrition, increased work of breathing due to airflow obstruction.

The results of the follow-up CPET are presented in Table 2.26. It can be seen that there is no significant difference in the follow-up (S2) CEPT responses compared with the initial i.e. S1.

DISCUSSION

A single episode of inhalation of MIC/toxic gas undoubtedly caused severe respiratory symptoms in almost 100% of the exposed population. Symptoms alone, however, could not tell the extent, severity, nature and prognosis of the respiratory problems. It is known that 4 human volunteers who inhaled 20 ppm methyl isocyanate for 5 minutes suffered from unbearable respiratory symptoms, but no lung disease[12]. Serial chest radiographs indicated the severity, extent and course of lung parenchymal and pleural lesions, but nothing precise about the airway disease nor of lung function and arterial blood gases. Post-mortem studies revealed findings in the extremes of the instantly fatal disease[4,13]. Open lung biopsy could be done in the subacute phase of the lung disease only in six severely exposed cases, making significant contribution to understanding the nature of the toxic gas related lung disase[14] (Chapters 1 and 8). Lung histology showed septal and pleural fibrosis with focal mesothelial proliferation, inflammation, destruction and in one case typically bronchiolitis obliterans, mononuclear cellular infiltration in bronchial and peribronchial tissues, peribronchial and peri-vascular fibrosis, inflammatory interstitial exudates and scarring. Similarly, 8 fibreoptic bronchoscopy studies in the sabacute phase revealed distorted airway humen, mucosal swelling, lymphoid hyperplasia, ulceration and patchy congestion[14] (Chapter 8). Broncho-alveolar lavage studies, 1-6 years after the exposure, showed evidence of increased number of alveolar macrophages and neutrophils and raised levels of fibronectin[14] (Chapter 4).

After the toxic gas leak, the Indian Council of Medical Research (ICMR), on the basis of immediate mortality data, classified the entire population of Bhopal into : (1) severely exposed = 32476, mortality 22/1000; (2) moderately exposed = 71917, mortality 1.33/1000;

(3) mildly exposed = 416869, mortality 0.2/1000; (4) unexposed = 311642. The present study was conducted on a carefully selected sample of 119 patients with no history of pre-existing lung or other disease, from the severely exposed area who had shown unequivocal evidence of very severe effects of the toxic gas – as described earlier. What is the total number of such cases in the entire severely affected area would never be known precisely. A word of caution the results of the present study should not be extrapolated to the affected population in other areas.

Serial studies of pulmonary function; arterial blood gases, acid base parameters and cardio-pulmonary responses to exercise test (CPET) have provided a deep insight into : (i) pathophysiology, i.e. structure-function relationship in lungs; (ii) better evaluation of the clinically not-so-well understood respiratory symptoms, especially dyspnoea and inability to work[6]; and (iii) indices for long term prognosis of the toxic gas related lung disease. The findings of the present study should be interpreted in the light of the following variables : (i) the time frame of the investigation, starting 128 days after the toxic gas exposure and concluding 1896 days after the exposure. It is thus possible that at the time of the initial study the acute lung lesions caused by a single one time inhalation of toxic gas would have undergone a process of healing or progression, naturally, or as a result of treatment and does not represent the acute phase; (ii) in the study group of 119 patients, approximately 50% suffered from malnutrition – judged from their BMI values[15]; This could have adversely affected their respiratory muscle efficiency and thereby aerobic work capacity. Thus, the present investigation as also all other similar investigations[14] (Chapters 1 to 8, 10) actually represent more or less a clinically stabilized toxic gas related lung disease. Only 10 cases could be studied in a relatively acute phase and again after 7 months which actually showed significant improvement of lung function in the recovery phase (Table 2.3).

The hallmark of the toxic gas related chronic lung disease in a more or less stable state is relatively irreversible obstruction to airflow in the central as well as peripheral/small airways, due to pathological narrowing of airways, in almost 90% of the cases in the present study – much more frequently observed in the small airways than the central airways.

FEV_1 has become the gold standard in the measurement of pathological airway narrowing[16,17] and correlates well with quality of life and exercise capacity[18], and also tests reversibility of airflow obstruction. In the present study, 33% had normal FEV_1, 33% showed mild reduction, 21% showed moderate reduction and 13% showed severe reduction of FEV_1. The diminished expiratory flow rates as residual volume approaches indicate involvement of small/peripheral airways less than 2 mm dia. This was the most common finding of the present study. For instance, only 10% cases had normal $FEV_{75\%}$, 15% showed mild reduction, 22% showed moderate reduction, while 53% showed severe reduction. Thus, the small airways, were the worst affected by inhalation of toxic gas; leading to constrictive bronchiolitis as seen in many other types of inhalational injury to lungs; there is a long list of such agents like ozone, nitrogen dioxide, sulfur dioxide, hydrogen sulphide, chlorine, ammonia, phosgene etc.[19-21]. For example, constrictive bronchiolitis after ammonia presents as cough and progressive dyspnoea beginning days to weeks after recovery from acute exposure[21]. MIC/toxic gas inhalation must have extensively involved the small airways with submucosal and peribronchial and perivascular fibrosis resulting in extensive narrowing and obliteration of bronchiolar lumen referred to as constrictive bronchiolitis. Many of the injurious inhalational agents involve adjacent alveolar units as well to produce organizing pneumonia (boop) to produce restrictive pulmonary and diffusion impairment. MIC and its

related toxic gases would be added to this long list of agents producing constrictive bronchiolitis.

The American Thoracic Society recommends that FEV_1 should be used to determine severity of airflow obstruction, and reduction of FEV_1/FVC% below 75% to confirm airflow obstruction[16]. Thus, in the present study FEV_1 was reduced in 66% cases while FEV_1/FVC% was reduced only in 13%. This is because FEV_1 would be reduced even in restrictive pulmonary disease.

The second most important finding in the present study was reduction of total lung capacity which means reduction of functioning alveolar units restricting the lung from expansion due to alveolo-pleural pathology. About 20% of the 119 patients had reduced lung volumes i.e. restrictive pulmonary impairment due to parenchymal lesions and fibrosis. A simpler way of diagnosing the type of pulmonary impairment has been used by some workers by referring to normal FVC (>75% predicted) and normal FEV/FVC% (>75%)[22]. Thus, of the 119 patients in the present study, 42.9% were normal, 20.2% showed restrictive, 11.8% obstructive and 25.2% showed restrictive cum obstructive (combined) pulmonary impairment.

Small airway dysfunction described above often leads to premature closure of airways during exhalation and alveolar air trapping[23] which leads to breathlessness on exertion due to impaired lung mechanics, even when FEV_1 and FEV_1/FVC% are normal. This was so in at least 65% of the cases. Total lung capacity was increased in 6% cases, suggestive of development of emphysema[24]. Bronchoreversibility test was positive in 6% cases, suggestive of development of asthma. It can not be said with certainty whether these people concealed the history of asthma or they were not aware of it, at the time of registration, or they developed asthma after the gas exposure.

The results of the single breath CO diffusion capacity of lungs were most interesting. Contrary to expectations, 70% showed normal values, 29% showed mild impairment, 1% moderate impairment and none showed severe impairment. These findings can be explained on the basis of patchy alveolar inflammation and fibrosis contiguous to the small airways. These findings exclude the possibility of diffuse interstitial lung disease, fibrosing alveolitis or diffuse interstitial fibrosis, because in these conditions reduced DLCO is the earliest abnormal finding[25,26]. Thus, except for a mild reduction of gas exchanging surface area in a small number of cases, the perfused surface area, thickness and integrity of the alveolocapillary membrane was preserved fairly well. Furthermore, in the present study there was no case with respiratory failure except one who had PaO_2 of less than 60 mm Hg, but no case of raised $PaCO_2$. This showed that even the airway dysfunction did not significantly disturb the ventilation – perfusion ratios in lungs at least under resting conditions.

The results of the 4 to 5 years follow-up study are even more interesting. After one year of the initial study, pulmonary function test values varied slightly on either side of the initial values but showed trends towards improvement even though slight, from the initial study. In the second and final follow-up, the pulmonary function test values did not show any significant change, even though FEV_1 values would have dropped marginally due to natural ageing effect[27]. The arterial blood gases also remained stable.

Prognostic Indices. All those patients exposed to toxic gas, more so the severely affected, should be followed up for decades. The various prognostic indices for detecting worsening lung status are – apart from the worsening clinical symptoms and HRCT – the falling FEV_1,

including rate of fall per year, increasing RV, increasing or decreasing TLC, decreasing DLCO, PaO_2 and increasing $PaCO_2$.

The truly crippling symptoms of "dyspnoea and inability to work" in the toxic gas victims could not be satisfactorily explained in all cases on the basis of their clinical profile and spirometry test[6]. During the performance of CPET, only 38 of the 80 patients stopped exercise due to severe breathlessness, while others stopped on account of mild to moderate breathlessness plus a host of other factors given in Table 2.23. At least 60% of the patients undergoing CPET had reduced FEV_1, reduced vital capacity and increased residual volume (RV); these would increase the work of breathing leading to breathlessness. Some cases might develop hypoxaemia on exercise which would add to dyspnea. Another explanation for breathlessness could be stimulation of type J receptors[28,29] – because of alveolitis[14] – during exercise (Chapter 4). The CO_2 production and oxygen uptake (R.Q.) data, Veq, VO_2/kg, O_2 pulse values indicated that the oxygen delivery and metabolic activity at tissue level were within normal limits. The minute ventilation, respiratory rate and heart rate responses showed that the patients had stopped exercise at a time when they still had plenty of respiratory as well as cardiovascular reserve in hand, meaning that the exercise was not always limited because of the cardio-respiratory system. There were several other factors which could have contributed to limiting aerobic work capacity. These were : psychogenic – leading to poor effort, physiological deconditioning, high level of anxiety, and protein nutritional deficiency. In the toxic gas exposed population, high incidence (22.6%) of neurotic depression and anxiety state, post-traumatic wounded minds and stress disorders have been reported[30,31]. It is interesting that follow-up CPET studies in a small number of cases showed neither improvement nor deterioration in exercise tolerance.

Several other investigators have studied extensively a very large number of toxic gas victims with 4-5 years follow-up[14] (Chapters 1, 3 to 8, 10). Broadly speaking,the results of these studies are in consonance with the results of the present study. For example, it is agreed that the main seat of the disease and the residual healed lesions were the airways followed by the pleura and lung parenchyma, producing the expected airflow obstructive and restrictive pulmonary impairment; that the perfused surface area, thickness and integrity of the alveolo-capillary membane were minimally disturbed, and respiratory failure was rare; that the toxic gas *per se* did not produce a progressive lung disease; that the pulmonary function improved in the first year after the exposure, after which this remained stable with only minor variations on either side of the observed values. Compared with other studies, the present study has evaluated the exercise test much more thoroughly. Minor differences between the observations of various studies were largely explained by the basic differences in the selection of study samples and sometimes the methodology used. Results of the long term follow up studies showed three patterns in different proportions : (i) majority of patient improved clinically, by chest radiographs as well as pulmonary function; (ii) a proportion of them showed a fluctuating course; (iii) a smaller proportion actually showed evidence of deterioration. It was interesting to note that in the present study and another major study[14] (chapter 1, 5-6) there was no significant difference in the pulmonary dysfunction and exercise test response between smokers and non-smokers. It was believed that the smokers would have been worst affected compared to non-smokers, but this was not so. Another significant difference in the observations of different studies was the incidence of asthma like response to inhaled bronchodilator. It is believed that this was due to difference in study samples selected rather than the true effect of the toxic gas *per se*. However, the possibility that the

toxic gas had initiated an asthma like disease, can not be ruled out. On the other hand, this needs to be pursued by proper investigation into the cause of bronchoconstriction.

Future projections. The findings of the present study and all other similar studies indicate that severely exposed population, who had shown clinical and radiological evidence of lung disease in the acute phase, are likely to be left with scars in the lungs, more specifically chronic constrictive bronchiolitis as is typically seen in inhalational injury of lungs[20]. This may predispose them to developing frequent episodes of chest infections, bronchospasm and in due course of time may lead to emphysematous changes. Thus, periodical medical evaluation by imaging including HRCT and pulmonary function testing may be required for those who continue to be symptomatic. Whether the residual fibrotic scars in lung would develop into carcinomas would remain to be watched[32,33].

CONCLUSIONS

A severe exposure to MIC and its toxic reaction products produced acute inhalational injury of airways and alveoli causing inflammation and increased capillary permeability leading to airway narrowing and interstitial/alveolar oedema. After healing of the acute injury, a proportion of patients were left with airway constricting lesions – more in the peripheral/small airways with less than 2 mm internal dia., than in the larger airways manifesting as constrictive bronchiolitis/bronchiolitis obliterans typically seen in many other inhalational injuries *e.g.*, nitrogen dioxide, ammonia, ozone, sulphur dioxide, phosgene *etc.* These patients were left with irreversible airflow obstructive disorders. The alveolar lesions adjoining the respiratory bronchioles healed with or without fibrosis, leading to restrictive pulmonary impairment as in cryptogenic organizing pneumonia. The perfused surface area, thickness and integrity of alveolocapillary membrane were only mildly compromised in a small proportion of cases. Arterial blood gases remained largely within the normal range.

ACKNOWLEDGEMENTS

The principal investigator, Prof.S.K.Jain, is indebted to Prof.A.S.Paintal (Late), then Director, Vallabhbhai Patel Chest Institute, University of Delhi for deputing him to start investigations at Bhopal and also provide support for equipment etc. from the DST Centre for Visceral Mechanisms.

Much gratitude is also due to Dean, Medical Faculty, Gandhi Medical College, Bhopal for granting permission and providing space to set up the pulmonary function, exercise test laboratory and providing technical assistant.

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Chapter 3

Radiological Manifestations in the Skiagram of Chest and Follow-up Studies of the MIC/Toxic Gas Affected Population

INTRODUCTION

The Radio-diagnosis Department of the Gandhi Medical College in Bhopal fully and actively participated in the investigation of the toxic gas induced lung disease, with the following objectives:

To provide routine diagnostic service for clinical management of patients.

1. To document chest radiographic changes in the acute phase immediately following the toxic gas exposure.
2. To conduct planned long term follow-up research studies of the chest radiographic patterns in the evolving chronic lung disease, and their correlation with pulmonary function tests and pulmonary disability.
3. To study elastic recoil, lung volumes and diaphragmatic excursions.

Patient Groups Studied

Group I 500 consecutive patients in the acute phase immediately following the toxic gas exposure reporting at the hospital with acute severe respiratory, eye and other symptoms.

Group II 9569 patients from the date of exposure to September 30, 1986 (5247 cases from outpatients and 4322 cases from MIC wards of Hamidia Hospital).

Group III From the ICMR registered cohort; in 3 phases.

- **Phase I** **(Period : February 1, 1985 to April, 1988**). 2709 subjects from the exposed areas and 1774 subjects from the unexposed/control areas.
- **Phase II** **(Period : May, 1988 to April, 1989).** 2500 cases were followed up. Out of these, 470 coded cases from exposed areas and 105 cases from control areas were studied in-depth.
- **Phase III** **(Period : May, 1989 to April, 1990).** 175 cases from Phase II in-depth study were further followed up in Phase III.

METHODOLOGY AND ANALYSIS OF DATA

Standardising Technique of Chest Radiographs

The only facility available for investigation was taking PA and lateral (if necessary) view of chest radiographs and bronchography in a few selected cases. All through the period of study, a standardized technique of taking and processing of radiographs was used to make comparisons valid. Lung volumes and respiratory excursions of diaphragm were measured by taking chest radiographs in maximal inspiration and maximal expiration.

In the post exposure period, upto September 30, 1986, the lung parenchymal opacities were recorded in 4 grades: (i) interstitial reaction; (ii) interstitial plus alveolar oedema; (iii) destructive lesions; (iv) pre-existing lung disease.

Modified ILO (1980) Classification
After September 1986, modified ILO (1980) classification was used.

Profusion. The severity of small parenchymal opacities is called profusion. These opacities comprise small rounded (nodular), micronodular, reticular and reticulonodular – classified according to the diameter of the predominant lesions : p – upto 1.5 mm q – 1.5 to 3 mm; r – exceeding 3 mm but less than 10 mm. The small linear or irregular opacities were defined according to size of lesions : s – fine; t – medium, coarse blotchy, on comparison with standard chest radiographs.

Profusion was graded into 4 basic categories : 0 normal; 1 (slight) – small opacities were definitely present, but few in number, while normal lung markings were visible; 2 (moderate) – small opacities were numerous while lung markings were partially obscured; 3 (advanced) – small opacities were very numerous while normal lung markings were totally obscured.

12 – Point scale for grading radiographs. The chest radiographs were read on a 12-point scale, which - recognizing the continuum – provides for intermediate grading between 0, 1, 2, and 3. For example, when there was no doubt about the grade of profusion, the categories were 0/0, 1/1, 2/2, 3/3. In between categories were recorded with a slash (/), e.g., 2/3, ½ - as the case may be. The main radiological findings were interstitial reaction showing profusion of various grades. In some cases, interstitial, perihilar/perivascular fibrosis, shrinkage of lungs and emphysema were seen. These were accordingly recorded.

Large opacities. An opacity or several small opacities with a total diameter between 10 and 50 mm was categorised as A. On the other hand, opacities exceeding A but less than the equivalent of right upper lobe, were categorized as B. If it exceeded B, i.e., the equivalent of right upper lobe, it was categorized as C.

Recording of Observations and Analysis of Data
As per the directives of the Project Advisory Committee (PAC) of the ICMR the skiagrams were read by a panel of experts; comprising three physicians and one radiologist. The reports of the skiagrams by the experts and the other relevant details of the patients were entered in the prescribed proforma. These were checked on all aspects and then sent to the computer section for analysis of the details of the abnormality.

Prior to computer analysis of data, validation exercise with reading of 100 skiagrams by the 4 experts was carried out. The findings showed “level of agreement” of four experts 46%; level of agreement of three experts 31%, level of agreement of two experts 23%.

The level of agreement between the three physicians - Prof.N.P.Misra, Prof.K.J.B.S.Gaur and Dr.S.C.Jain - was : in only 2% of the skiagrams the opinion of all three physicians differed. As far as the difference of opinion between radiologist and physicians was concerned it came out to be 16%; these skiagrams were read together by the physicians and the radiologists and differences sorted out. Thus, all skiagrams collected and read in this manner till March 1988 were sent to “Computer Center” for analysis. Further, as recommended by the PAC, out of the abnormal skiagrams reported by the panel of experts, 176 skiagrams randomly selected were evaluated by Prof. Sneha Bhargava, Director and Head, Department of Radiology, AIIMS, New Delhi. 89% of the observations made by the expert group were found to be in complete agreement.

The observations on chest radiographs were also correlated with clinical features and pulmonary function test values.

OBSERVATIONS

Patient Group I

In this series, chest radiographs of 500 consecutive patients (263 males, 237 females) taken in the immediate post exposure period were analysed and the findings are presented in Table 3.1. Clinically, they all had severe symptoms : cough, expectoration, breathlessness, chest pain, inability to do work, swelling of eyes and gastro-intestional symptoms.

Table 3.1 X-ray Changes and their Distribution in 500 Chest Skiagrams in the Acute Phase

S. No.	Changes in skiagram chest	No. of cases	Bilateral involvement	Zonal distribution			Unilaternal involvement	Zonal distribution		
				Upper	Mid	Lower		Upper	Mid	Lower
1.	Only interstitial reaction	207 (41.2%)	168 (33.6%)	17	43	108	39	9	11	19
2.	Interstitial (+) alveolar reaction	203 (40.6%)	184 (36.8%)	13	24	53	19	2	5	12
3.	Destructive lesions (pneumonitis, cavitation, subcutaneous emphysema, pneumo-mediastinum, pleural effusion)	40 (8%)	27	15	6	6	13	6	3	4
4.	Pre-existing disease (tuberculosis, COAD, etc.)	36 (7.2%)	21	6	2	13	15	7	6	2
5.	Unilateral * opacity	3 (0.6%)	-							
6.	No abnormality	11 (2.2%)	-							

*whole hemithorax was opaque.

It can be seen from Table 3.1 that only 11 (2.2%) cases had normal chest radiograph, while 7.2% were suspected to have pre-existing lung disease. All others showed radiological evidence (majority bilateral) of interstitial shadowing, alveolar oedema and pneumonitis. The x-ray changes gradually cleared with time in most cases, leaving residual streaky, reticulonodular, punctate, fibrotic opacities in a proportion of them. It is noteworthy that similar chest radiographic findings have been described in cases who accidentally inhaled high concentration of toxic, irritant gases like ammonia, nitrous oxide, chlorine, phosgene etc. Thus, the x-ray changes in toxic gas (MIC) exposed population may not be specific to methyl isocyanate and its reaction products.

It may be concluded that 98% of all toxic gas exposees who suffered severe respiratory symptoms in the acute phase also had abnormal chest radiographs. However, during the long term follow-up most skiagrams showed clearance, although some of these were left with residual lesions.

Patient Group II

Table 3.2 Shows Distribution of Radiological Findings in Patient Group II Study

	Total number of patients studied	**9569**
	Findings in chest skiagram	Number (%)
1.	Normal chest radiographs	5306 (55.4)
2.	Interstitial reaction	1963 (20.5)
3.	Interstitial + alveolar oedema	203 (2.1)
4.	Pneumonitis, collapse, consolidation, pneumomediastinum, pneumothroax, pleural effusion	778 (8.3)
5.	Suspected pre-existing lung disease	1319 (13.7)
	Total	9569 (100)

It can be seen from Table 3.2 that of the 9569 patients of group II, 55.4% had normal chest radiographs, 13.7% had pre-existing lung disease, 30.9% had pulmonary lesions – mostly interstitial reaction.

Six hundred seventy-two skiagrams were analysed according to modified ILO (1980) classification. 511 of these were found to be normal (0/0), while the remaining 161 showed abnormalities ranging from 1/1 to 3/3. Thirty-three cases (4.9%) were suspected to have pre-existing lung disease, i.e., pulmonary tuberculosis = 24, and disturbed cardiothoracic ratio = 9. Out of the 100 Control cases included for comparison, 88 (88%) were found to be normal (0/0), while remaining 12 (12%) had abnormalities ranging from 1/1 to 3/2. In the Control group, pre-existing lung disease was found in 12 (12%) cases (pulmonary tuberculosis = 9, disturbed cardiothoracic ratio = 3.

Diaphragmatic excursions, elastic recoil and volumes of lung were estimated in 40 patients from the toxic gas affected area and 10 subjects from the control area. The normal elastic recoil in subjects from control area was found to be about 3 cm, compared with 0 to 2 cm in 70% of the patients from the affected area. Excursion of the dome of diaphragm in the control area was found to be 0.7 to 1.8 cm, while in 90% of the patients from affected areas it was below this range. The lung volumes in the affected population was found to be lower than the corresponding values in the subjects from control areas. It may be noted that this is a very small number of observations in a randomly selected group and therefore cannot be extrapolated to the general population.

Radiological Spectrum of Lung Changes in Toxic Gas Exposed Compared with Control Population in Phase I (February 1, 1985 to April 1988) Study

Phase I study included two groups of patients : (i) referred from out-patients and MIC Ward of Hamidia Hospital; (ii) from ICMR cohort of the "Epidemiological Study of Long Term Effects of Toxic Gas on Respiratory System". The chest radiographs were analysed by a panel of three physicians and one radiologist and the data were sent to the Computer Center for analysis. The observations by this panel were validated by an outside expert as described in Methodology.

In Phase I total number of cases investigated upto April 1988 were 6049. However, during the computerized validation programme, only 4483 cases [2709 (60.4%) exposed, 1774 (39.6%) control] were found complete in every respect for computer analysis. The data are presented in Tables 3.3 to 3.7.

Table 3.3 Phase I Study : Gender-wise and Age-wise Distribution of Subjects from Affected and Control Areas

	Affected areas														
Age group	**Mild**			**Severe**			**Moderate**			**All areas**			**Control areas**		
Years	**M**	**F**	**Total**	**M**	**F**	**Total**	**M**	**F**	**Total**	**M**	**F**	**Total**	**M**	**F**	**Total**
0 – 10	29	26	55 13.8	83	64	147 15.0	103	101	204 15.2	215	191	406 14.9	167	129	296 16.6
11 – 20	28	33	61 15.36	83	101	184 18.8	101	163	264 19.7	212	297	509 18.7	126	188	314 17.7
21-30	31	52	83 20.90	114	134	248 25.4	107	181	288 21.5	252	367	619 22.8	180	400	580 32.6
31-40	31	51	82 20.65	90	66	156 16.0	95	126	221 16.5	216	243	459 16.9	121	187	308 17.3
41-50	20	28	48 12.09	60	58	118 12.1	77	94	171 12.7	157	180	337 12.4	56	87	143 8.0
51-60	24	24	48 12.09	48	36	84 8.6	71	51	122 9.1	143	111	254 9.3	35	53	88 4.9
Above 60	12	8	20 5.03	27	10	37 3.7	38	30	68 5.0	77	48	125 4.6	26	19	45 2.5
Total	175 44%	222 56%	397	505 51.5%	469 48.5%	974	592 44.2%	746 55.8%	1338	1272 46.9%	1437 53.1%	2709	711 40%	1063 60%	1774

M = male F = female

It can be seen from Table 3.3 that both genders and all age groups are uniformly distributed in the affected (mild, severe and moderate) group compared with control group.

Table 3.4 Chest Radiographs Showing Tuberculosis and Interstitial Reaction in the Affected Group Compared with Control Group

Affected age group	Total cases			Pulmonary tuberculosis			Interstitial reaction		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
< 21	427	488	915	13	15	28	16	27	63
21 – 30	252	367	619 22.8	9	12	21 12.6	19	39	58 21.3
31 – 40	216	243	459 16.9	23	15	38 22.8	29	29	58 21.3
41 – 50	257	180	337 12.4	15	16	31 18.6	27	23	50 18.3
Above 50	220	159	379	32	16	48	47	36	83
Total	1272 46.9	1437 53.1	2709	92(7.2%) 55.4	74(5.1%) 44.6	166(6.1%)	118(9.3%) 43.3	154(10.7%) 56.7	272 (10.0%)
Controls Age Groups									
< 21 yrs	293	317	610	7	7	14	3	1	4
21 – 30	180	400	580 32.6	4	5	9 17.6	7	14	21 23.2
31 – 40	121	187	308 17.36	7	5	12 23.5	9	13	22 24.4
41 – 50	56	87	143 8.06	3	1	4 7.6	9	9	18 20.0
Above 50	61	72	133	8	4	12	12	13	25
Total	711 40.0	1063 60.0	1774	29 56.8	22 43.2	51(2.9%)	40(5.6%) 44.4	50 55.6	90(5.1%)

Table 3.4 shows that in the affected group 6.1% of the chest radiographs showed evidence of pulmonary tuberculosis, and 10% showed interstitial reaction. The corresponding figures in the control group were 2.9% and 5.1% respectively. No significant difference was observed between males and females.

The following important findings were recorded by computer analysis (see Tables 3.3 to 3.7):

1. The maximum number of cases belonged to the age group of 21-30 years: 22.8% and 32.6% in the affected and control groups respectively.
2. The main abnormality was interstitial reaction.
3. 53.1% of the affected groups were females and 46.9% were males.
4. Of the total number of affected population showing interstitial reaction, 89.9% had pulmonary disability and 72.5% showed abnormal PFT findings.
5. In the control areas who had interstitial reaction had 18.9% pulmonary disabilities and 43.2% abnormal PFT findings.
6. On detailed analysis according to severity of exposure, in severely affected areas, 92.6% had pulmonary disabilities and 72% abnormal PFT findings.
7. In moderately affected areas, out of 106 cases who had interstitial reaction, 92.4% had pulmonary disability and 78.3% showed abnormal PFT findings.
8. In mildly affected areas, out of 30 cases who had interstitial reaction, 73.3% had pulmonary disability and 53.4% showed abnormal PFT findings.

The total number of cases having interstitial reaction were further subgraded according to 1980 ILO classification of pneumoconiosis which is presented in Tables 3.5 to 3.7.

Table 3.5 Phase I Study : Radiological Findings

S.No.	Radiological findings	Severe		Moderate		Mild		Total Affected		Control	
		No.	%	No.	%	No.	%	No.	%	No.	%
1.	Normal	674	70.1	946	72.21	246	68.3	1866	70.92	1457	84.17
2.	Pulmonary TB	68	7.07	78	5.98	20	5.55	156	5.92	51	2.94
3.	Emphysema	02	0.93	14	1.06	02	0.5	25	0.95	04	0.73
4.	Interstitial Reaction	92	9.57	132	10.07	63	17.5	287	10.90	87	5.02
	A. 0/1	38	41.30	36	27.2	09	14.2	83	28.9	22	25.2
	B. 1/0	36	39.1	77	58.3	31	49.2	144	50.17	43	75.4
	C. 1/1	18	19.5	18	13.6	23	36.5	59	20.5	19	21.8
	D. ½	0	01	0.75	0	0	0	01	0.34	03	3.6
5.	PBF	38	2.08	60	4.58	12	3.33	110	4.18	12	0.69
6.	Total ABN	287	29.8	364	27.7	114	31.6	765	29.08	274	15.82
		961		1310		360		2631		1731	

PBF = Peribronchial fibrosis ABN = Abnormal

Table 3.6 Affected Group : Radiological Findings, Pulmonary Disability and PFT Findings.

Radiological	Total	Pulmonary disability		PFT Findings					
		Positive	Negative	Comb.	Obst.	Rest.	Total	Normal	Total
Normal	1095 (58.27)	954 (87.1)	141 (12.9)	64	34	489	587 (56.2)	480 (43.8)	1067
Total abnormal	455 (41.73)	408 (89.6)	47 (10.4)	67	21	228	316 (70.1)	136 (29.89)	452
Pulmonary TB	100 5.32	87 (87.0)	13 (13)	20	7	42	69 (70.6)	29 (29.0)	98
Interstitial	218 11.60	196 (89.9)	22 (10.1)	29	11	117	157 (72.5)	60 (27.5)	217
A. 0/1	61 28.0	57 (93.4)	4	3	3	34	40 (65.6)	21 (34.4)	61
B. 1/0	104 47.7	92 (88.4)	12	14	6	62	82 (78.8)	22 (21.15)	104
C. 1/1	33 15.1	30 (90.9)	3	6	2	12	20 (60.7)	13 (39.3)	33
D. ½	-	-	-	-	-	-	-	-	-
Emphysema	12	11 (91.6)	-	4	1	3	8 (72.8)	3 (27.2)	11
Total	1550	1362 (87.9)	188 (1.21)	131	55	717	903	616 (40.5)	1519

PFT = Pulmonary function test

Table 3.7 Control Group : Radiological Findings, Pulmonary Disability and PFT Findings

Radiological	Total	Pulmonary Disability		PFT Findings					
		Positive	Negative	Comb.	Obst.	Rest.	Total	Normal	Total
Normal	704 84.0	76 10.7	628	12	25	91	128 18.2	576 81.8	704
Abnormal	134 16.0	23 17.16	111	6	8	29	43 32.1	91 67.9	134
Interstitial	58 6.92	11 18.9	67	2	3	20	25 43.2	33 56.8	58
A. 0/1	16 27.3	0 0.0	16	1	1	3	5 31.2	11 68.75	16
B. 1/0	39 63.7	9 23.0	28	2	3	14	19 51.4	18 48.6	39
C. 1/1	16 27.5	3 18.7	13	0	-	4	4 25.0	12 75.0	16
D. ½	2	0 0.0	2	-	-	2	2	-	2
Emphysema	3 35.0	0 0.0	3	0	0	0	0	3	3
Pulmonary TB	17 2.02	4 23.5	13	1	1	3	5 29.5	12 70.5	17
Total	838	99 11.8	739	18	33	120	171 20.5	667 79.5	838

2500 cases from the ICMR registered cohort included in Phase I study were reviewed. Out of these 444 coded cases from affected/exposed areas and 105 coded cases from control areas were taken up for in-depth study. Both groups were matched for age and gender distribution. Skiagram chest were read as described above and the findings are presented in Table 3.8.

Table 3.8 Categorisation of Cases in Phase II and Phase III Studies

Findings	Affected Area N = 444	Control Area N = 105
No abnormality detected	206 (46.4%)	75 (71.4%)
Reticular, reticulonodular, interstitial shadows	*115 (25.9%)	9 (8.6%)
Chronic bronchitis, perihilar, peribronchial fibrosis	98 (22.1%)	13 (12.4%)
Destructive lesions : tuberculosis etc.	13 (2.9%)	6 (5.7%)
Cardiac abnormalities	12 (2.7%)	2 (1.9%)
Total	444 (100%)	105 (100%)

Out of 115 cases from affected areas showing interstitial shadowing, there was evidence of Large airway obstruction (35%), small airway obstruction (46%), restrictive cum obstructive abnormality (3%), restrictive impairment (2%), and normal lung function (14%).

The interstitial lesion cases (115 in number) were further followed up : 6 cases 4 times, 23 cases 3 times, 55 cases 2 times. Out of these 115 cases 32 cases were normal when they were x-rayed for the first time; of these 28 cases became abnormal in their second follow-up and the remaining 4 cases became abnormal in 3rd follow-up.

Pulmonary function test data are not available in the Control group.

PHASE II AND PHASE III STUDY (1988 – 1989-1990)

The study samples were taken from ICMR 03 Project In-depth Study. The cases were categorized (1 to 5) on the basis of chest radiograph and pulmonary function test findings (PFT).

Category	Symptoms	Chest radiograph findings	PFT findings
1.	No symptoms	Normal	Normal
2.	Symptomatic	Normal	Normal
3.	Symptomatic	Abnormal	Normal
4.	Symptomatic	Normal	Abnormal
5.	Symptomatic	Abnormal	Abnormal

Phase II study included 188 cases from in-depth study as described above. The results showed –

No. of skiagrams	188
Normal skiagrams	95
Abnormal skiagrams	81
Repeat skiagrams	12

1. Interstitial reaction
2. Destructive lesions and pre-existing diseases
3. Cardiac abnormality
4. Pulmonary vascular abnormality

Interstitial Reaction

- Reticulonodular opacities
- Micronodular opacities
- Reticular opacities
- Linear opacities

Destructive and Pre-existing Lesions

- Pulmonary tuberculosis or primary complex
- Pleural thickening or effusion
- Emphysema, chronic bronchitis, collapse, consolidation, pneumonitis calcification etc.

The Main Findings of this Study are:

The studies were performed in 10 to 50 years old and above.

- The abnormality in chest skiagrams was observed most commonly in category III and V - 50% and 47.7% respectively.
- Of the 43% abnormal cases, males were affected more (25%) than females (18%).
- Males were affected more in category III (30.9%) while females were affected more in category V (22.72%).

The main radiological abnormality in the chest skiagrams of the in-depth study of 188 cases was interstitial reaction, followed by pulmonary tuberculosis or primary complex and pulmonary vascular abnormality.

Amongst the 43% of abnormal chest skiagrams:

- 3.7% cases were of pulmonary tuberculosis or primary complex,
- 5.31% cases were of pulmonary vasculature abnormality,
- The highest percentage (36.36%) of interstitial reaction was seen/found in category V.
- The highest percentage of pulmonary tuberculosis was in category III (9.52) and 4.54% in category V.

Correlation between age group, interstitial reaction, and pulmonary tuberculosis.

- Incidence of interstitial reaction was more in the age group 31-40 years.
- Females were more affected in age group 31-40 years.
- Pulmonary tuberculosis was more common in males.
- Interstitial reaction was highest in category V, followed by category III and category I respectively.
- Pulmonary tuberculosis prevalence was highest in category III followed by category V and category I.

PHASE III STUDY

The cases of in-depth study which were included in Phase II study were further followed up in Phase III study from Project 03.

Total number of cases	175 (males 89, females 86)
Normal skiagrams	88
Abnormal skiagrams	78
Repeat	09

The important findings of this study are:

The studies were performed in the age group of 10 to 50 years.

1. The abnormality in chest skiagrams was observed mostly in category III (70.9%) followed by category V (40.9%) respectively.
2. Of the 175 cases followed up, 44.57% cases were abnormal and 55.43% cases were normal.
3. In the 44.57% abnormal cases males were affected more (25.1%) than female (19.4%).
4. Males were affected more (45.16%) in category III while the highest percentage of abnormality (25.8%) in females was also observed in category III.

The main abnormality in the chest skiagrams was again interstitial reaction (33.14%).

1. The percentage of interstitial reaction was highest (51.65%) in category III followed by (36.36%) category V.
2. The percentage of pulmonary tuberculosis (6.4%) was highest in category III .

Correlation between age group and interstitial reaction.

1. Incidence of interstitial reaction was more in age group 31-40 years.

CONCLUSIONS

The chest radiographs of 91% of the toxic gas exposed patients with severe respiratory symptoms showed evidence of interstitial/alveolar oedema and pneumonitis in the immediate post-exposure period. The lung lesions showed signs of clearance, leaving residual streaky, interstitial reaction and fibrotic opactities.

In a large cohort follow-up study on long term basis, approximately 40% of cases showed interstitial reaction in chest radiographs – reticular, reticulomodular, micronodular, linear peribronchial and prevascular fibrotic opacities. These changes were associated with pulmonary disability and pulmonary function impairment.

Similar chest radiographic findings have been reported in inhalational injuries due to ammonia, nitrogen dioxide etc. Thus, MIC induced lung changes may be only of a non-specific nature.

Chapter 4

Broncho-Alveolar Lavage (BAL) Studies in MIC/Toxic Gas Affected People at Bhopal

INTRODUCTION

As described under clinical profile of the toxic gas affected population, 99% of the exposees had instantly developed respiratory symptoms – the severity of symptoms was perhaps determined by the concentration of the inhaled gas[1,2]. Early autopsy studies on deaths occurring immediately or during the first four weeks have established that the immediate cause of death was asphyxia as a result of acute lung injury, pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS). Similarly, autopsies during the 1 to 4 month period and beyond showed evidence of pulmonary oedema and exudative lesions; and diffuse interstitial lung disease[3].

The survivors in the exposed population continued to suffer in large proportions from breathlessness, cough and chest pain. Many a time these symptoms could not be explained on the basis of conventional chest radiograph and pulmonary function test results. Furthermore, population based long term epidemiological studies (1985-94) showed high prevalence rates of respiratory symptoms – depending upon the severity of exposure. These symptoms improved with time[4]. It thus seemed likely that the inhalation of toxic gas produced alveolitis which might take a long time to resolve or heal. Therefore, broncho-alveolar lavage (BAL) was performed on a small group of patients from exposed population to find evidence of inflammatory and immune effector cells and their mediators in the lower respiratory tract[5]. Being a somewhat invasive procedure, it was not possible to perform BAL on a randomly selected sample, nor could this be done on a large number of patients. Some of the patients with persistent symptoms were approached, asking if they would be willing to undergo this procedure. Those who consented were taken up for this study.

THE PROSEDURE

BAL protocols were approved by the ICMR, New Delhi. The procedure was clearly explained to the patient in local language and informed consent was obtained in each case.

Pre-lavage assessment included: detailed clinical history and physical examination; PA chest radiograph; 12-lead ECG; routine blood test, and a reference to pulmonary function test laboratory for complete assessment. All patients with pre-existing lung disease were excluded from the study. Thus, from amongst those who had willed for undergoing BAL, fifty-six patients (51 males, 5 females), were subjected to the procedure, on out-patient basis, at the Hamidia Hospital, Bhopal.

BAL studies were carried out between February 1987 to March 91. Patients were pre-medicated intravenously with valium (5-10mg) and intramuscularly with atropine (0.8mg). Four percent xylocaine spray was used to anaesthetize the oropharynx and 5 percent dextrose was administered intravenously during the precedure. Flexible fibreoptic bronchoscope with an inner diameter of 2.6 mm (Olympus BF type IT 10, S.No. 2511484) was used for bronchoscopy and bronchoalveolar lavage. Usually, the trans-nasal passage was used, but

occasionally the bronchoscope was passed transorally. The lavage was usually done from three sub-segments, viz., right middle lobe, lingua and left lower lobe. The tip of the bronchoscope was wedged in a sub-segment. BAL was performed with 300 ml sterile 0.9 percent saline at room temperature. One hundred milliliters of sterile saline in five 20 ml aliquots was infused through the bronchoscope into each of the three lobes in the lower respiratory tract. After each aliquot was infused a gentle suction using 50-100 mm water negative pressure with the usual clinical suction apparatus was applied to recover the infused fluid containing cells which was collected in specimen traps. The fluid obtained by lavage was pooled in a sterile plastic cup (Falcon-Plastics, Oxford, CA). The bronchoscopy and BAL procedure were done under continuous cardiac monitoring. Supplemental oxygen was administered during and 1-2 hr following the lavage. All individuals were observed for 3-4 hrs after the procedure. There were no complications during the entire procedure in any of the patients.

Immediately after the lavage, the fluid was filtered through three layers of sterile surgical gauze and the volume was measured accurately. Cells were evenly resuspended by repeated aspirations with a 10 ml pipette. An aliquot was removed for cell count. Rest of the fluid was centrifuged and preserved for biochemical and immunological studies. The cells recovered by lavage were counted on a haemocytometer, using the unconcentrated lavage fluid. Nitrocellulose filters 25 mm in diameter with 5 μm pores (SMWP – 025-00, Millipore Corporation, Dedford, MA) were pre-soaked in absolute alcohol for 5 sec and mounted above a paper pad (AP-10-025-00, Millipore Corp.), in a 15ml graduate funnel with a fritted glass base (xx-100-25-14, Millipore Corporation. The filter was then washed with 15 ml of 0.9 percent sodium chloride. 2x105 lavage cells were added to the funnel and the filter was washed with 15 ml of absolute alcohol. The filters were then removed from the funnel apparatus, mounted on to 25 x 75 mm microscope slides using “Bell Clips” (Bell Product Co).

Cells collected on filters were stained with haematoxylin and eosin. The filters mounted on glass slides were washed in tap water (5min), and distilled water (1 min) and stained in Harris hamatoxyline (30 sec). Filters were ‘blued’ by washing in lukewarm tap water for at least 20 min. After bluing, filters were dipped in 50 per cent ethanol (1min), and 80 percent ethanol (91 min), and counter-stained in eosin (2.5). The filters were then dipped in 3 changes of absolute alcohol (1 min) each, one change of 2 propanol (2 min) and three changes of xylene (1-2 min each), until they are transparent and mounted on 25 x 75 mm glass microscope slides under glass coverslips using permount. Using oil immersion of a microscope alveolar machrophages, lymphocytes, neutrophils and eosinophils were identified and 400 cells were counted from each preparation for deriving the differential counts. Bronchial epithelial cells counted were always less than 5 percent.

BAL studies were repeated in 21 patients. However, the data from one patient was excluded because of persistent residual effects of previously performed bronchogram in this patient; thus, BAL results from 20 patients were available for analysis. BAL was repeated thrice in 4 patients, 4 times in the 5th patient. One patient had poor recovery of lavage fluid at the time of 3rd lavage.

Ideally, lavage should have been done in normal individuals not exposed to ‘toxic’ gas at Bhopal. However, this could not be done because of the difficulty in obtaining consent from such subjects. In the present study, therefore, the results of lavage performed on 17 non-

smoking individuals from Madras (Chennai) (Vijayan. V. K., unpublished data) were used for comparison. None of these subjects had respiratory symptoms or abnormal physical findings, and all had normal chest x-ray and normal pulmonary function test values. None of the subjects were on any medication.

As per the recommendations of the ICMR Project Advisory Committees in 1988 and 1989, BAL samples were transported from Bhopal to the Department of Medicine, AIIMS, New Delhi for estimation of fibronectin levels, under the supervision of Professor J.N.Pandey. Fibronectin values were measured in BAL fluid by single radio-immunodiffusion (LC-Partigen plates-Behring, West Germany). Albumin estimations in BAL fluids was done by spectrophotometric method. Fibronectin values were expressed as μg/mg albumin. Fibronectin levels were estimated in 63 samples from patients and 10 samples from normal subjects.

Severity of Exposure

As the degree of exposure to the gas may not be the same in all individuals, the patients were categorized into three groups according to the severity of exposure:

Severe exposure. If one or more of the members of the family died due to the toxic gas exposure or the patient had severe ophthalmic and respiratory symptoms, requiring immediate medical help with assistance from others, the patient was classified as having severe exposure.

Analysis of Data

Moderate exposure. After exposure to the gas, if the patient developed respiratory symptoms and required immediate medical relief, the patient was classified as having moderate exposure.

Mild exposure. After exposure, if the patient developed respiratory symptoms, but did not seek immediate medical relief because of mild nature of symptoms, the patient was classified as having mild exposure.

All observations between groups were compared using the two tailed student ‘t’ test and also with Mann-Whitney U test and the results were found to be similar. Paired results from individuals were compared using paired t-test. The trend Chi square test was applied to see whether the level of exposure had any trend effect on the number of cells. Parson’s product moment correlation was used for correlations.

RESULTS AND DISCUSSION

While the one-time toxic gas exposure took place on December 3, 1984, BAL studies were carried out between February 1987 and March 1991 i.e. more than 2 to 6 years after the incident.

Bronchoalveolar lavage results from a selected sample on voluntary basis of 51 males and 5 females were included in the analysis. The mean age was 35.6 + 10.1 yr. (range 18-60 year). There were 6 patients with mild exposure, 10 with moderate exposure and 40 with severe exposure. Ten severely exposed and three moderately exposed patients were smokers. Rhonchi and/or rales were detected in 9 patients (severe 8, moderate 1, mild 0). All mildly exposed patients had chest radiographs and pulmonary function test results within the normal range. Five of the moderately exposed patients had radiographic abnormality of 1/0 or 1/1 (ILO, 1980 classification) and four patients had obstructive ventilatory impairment.

Radiographic abnormalities of 1/0 to 2/2 were observed in 29 of 40 severely exposed patients. Eleven patients revealed obstructive and eight had restrictive ventilatory impairment in the severely exposed group. The total and differential leukocyte counts and electrocardiograms were within normal limits in all patients. Results of arterial blood gases were available in 19 patients (mild/moderate 6 and severe 13). Arterial hypoxemia (PaO_2<80mmHg) was present in 6 patients (mild/moderate 1, severe 5). Hypocapnia (PaCO2<35mmHg) was present in 2 and hypercapnia (PaCO2 >45mmHg) in one patient. All samples had normal pH values.

The mean values of total cell counts in mildly and moderately exposed patients were not significantly different (p>0.1) from Madras (Chennai) 'Normals' (Table 4.1). The mean differential cell counts in mildly exposed patients were similar to Chennai 'Normals'. However, the mean macrophage percentage was significantly higher (p<0.001) in moderately exposed subjects. Severely exposed patients had significantly elevated (p<0.01) total cell count in the lower respiratory tract compared to normals. This was true whether all individuals or only severely exposed non-smokers were considered. However, the proportion of different type of cells recovered were similar to that of 'normals'.

The absolute numbers of different type of cells (total cells times differential percentages) are given in Table 4.2. Among the inflammatory and immune effector cells recovered from the lower respiratory tract, macrophages showed a significant rise in moderately exposed subjects. There was a significant rise in mean values of alveolar macrophages and neutrophils in severely exposed subjects, whether all individuals or only non-smokers or smokers were considered.

The range of total cells (x106/d1) recovered from the lower respiratory tract was 5.5 to 13.8 in mildly exposed, 13.0 to 34.1 in moderately exposed, 9.6 to 71 in severely exposed (non-smoker) and 21 to 136 in severely exposed (smoker) patients. Fifteen (50%) of 30 severely exposed (non-smokers) and 9 (90%) of 10 severely exposed (smokers) had more than 2-fold increase in cells in the lower respiratory tract, whereas only two (12.5%) of 16 mildly and moderately exposed patients had more than 2-fold increase. With increasing severity of exposure and with history of smoking, there was a tendency for a higher proportion of patients to have increasing cellularity in the lower respiratory tract and this trend was statistically significant (p<0.001).

Table 4.1: Total and Differential Cell Counts in Lower Respiratory Tract (Mean ± SD)

Group	**Total cells ($x10^6$/d1)**	**M %**	**L %**	**N %**	**E %**
Normal (Madras) (n = 17)	15.3 + 6.8	83.9 + 6.4	14.4 + 6.5	0.7 + 0.8	1.0 + 1.1
Mild exposure (n = 6)	10.7 + 3.2	86.8 + 5.4	12.3 + 4.9	0.8 + 0.98	0
Moderate exposure (n = 10)	21.1 + 6.4	94.3 + 3.9**	4.1 ± 3.6**	1.5 + 2.0	0.1 + 0.3
Severe exposure (n = 40)	35.8 + 24.4*	87.8 + 10.7	9.9 + 10.0	1.7 + 2.0	0.6 + 1.5

M = Macrophages, L = Lymphocytes, N = Neutrophils, E = Eosinophils, P Values * <0.01, ** 0.001 as compared to normal group

Table 4.2: Mean Absolute Values of Inflammatory and Immune Effector Cells (Mean ± SD)
Cells ($x10^6$ / dl)

Group	M	L	N	E
Normal (n = 17)	13.2 + 5.6	2.4 + 1.5	0.1 + 0.1	0.1 + 0.1
Mild exposure (n = 6)	9.38 + 3.12	1.33 + 0.47	0.07 + 0.08	0
Moderate exposure (n = 10)	19.75** + 5.57	0.86 + 0.83	0.40 + 0.72	0.04 + 0.10
Severe exposure (Non-smokers) (n = 30)	25.13** + 13.69	3.11 + 3.32	0.46* + 0.64	0.2 + 0.4
Severe exposure (Smokers) (n = 10)	53.76[!!] + 36.36	2.16 + 2.03	0.66[!!] + 0.51	0.12 + 0.29

p Values *<0.05, **<0.01; [!!]<0.001 as compared to normals

Since accumulation of inflammatory cells in the alveolar structures is referred to as alveolitis[7], the observation of increased cells in severely exposed patients studied 1-6 year after exposure suggests that a proporton of these patients had persistent alveolitis. The significant increase in macrophages and neutrophils in severely exposed subjects further suggest that these subjects had macrophage/neutrophilic alveolitis. The observation of increasing cellularity in the lower respiratory tract, as the severity of exposure increases and also the higher total cells in severely exposed smokers, compared to non-smokers suggest that smoking is a possible risk factor.

Table 4.3: Initial and Repeat Lavage Results (Mean ± SD)

Group	Total cells ($x10^6$ / dl)	M %	L %	N %	E %
1st Lavage (n = 20)	28.0 + 15.2	88.3 + 8.0	10.2 + 7.6	1.1 + 1.4	0.4 + 1.8
2nd Lavage (n = 20)	31.6 + 20.3	87.7 + 7.0	8.0 + 5.1	3.6* + 4.5	0.8 + 1.6

* p = 0.02

Table 4.4: Absolute Numbers of Different Types of Cells (Mean ± SD)
Cells (x 10^6 / dl)

Group	M	L	N	E
1st Lavage (n = 20)	25.3 + 15.3	2.4 + 2.0	0.3 + 0.3	0.1 + 0.4
2nd Lavage (n = 20)	27.6 + 17.8	2.6 + 3.3	1.2* + 2.1	0.2 + 0.4

*p = 0.05

BAL was repeated in 20 patients in whom the first study was done 1-3 yrs post-exposure. The results are shown in Tables 4.3 & 4.4. During 2nd lavage (2-6 years after exposure) the total inflammatory cells in the lower respiratory tract (15.8 + 6.8 vs 31.6 + 20.3, $p<0.001$) and absolute recovery of alveolar macrophages (13.2 + 5.6 vs 27.6 + 17.8, $p<0.01$) continued to be significantly higher than the normal values. In addition, there was a significant rise in neutrophils in the lower respiratory tract during 2nd lavage. Another interesting finding was the observation of significant fall in lymphocyte percentage (normal 14.4 + 6.6; vs 8.0 + 5.1, $p<0.01$) during 2nd lavage, though the absolute numbers of lymphocytes did not show any change (normal 2.4 + 1.5 vs 2.6 + 3.3, $p>0.2$). The persistence of expanded number of

alveolar macrophages and abnormal accumulation of neutrophils 2-6 years after the exposure suggest that the initial macrophagic alveolitis is progressing to macrophage-neutrophilic alveolitis as time passes[8-13]. The significance of the reduced proportion of lymphocytes during 2nd lavage is not understood.

Table 4.5: Results of 3 or 4 Lavages in 4 Subjects

Group	Total cells ($x10^6$/dl)	M %	L %	N %	E %
Subject 1					
20 March 1986	51.3	92	7	1	0
25 February 1987	64.4	96	3	1	0
23 February 1989	12.5	66.5	0.5	32.5	0.5
17 February 1990	23.6	95	3	1	1
Subject 2					
16 March 1986	33.4	76	23	1	0
28 February 1987	18.1	88	10	2	0
1 March 1989	14.4	52	37	9	2
Subject 3					
9 December 1985	15.0	84	13	3	0
25 February 1989	37.9	56	4	40	0
2 March 1989*					
RML	56.8	82	12	3	3
Ling.	68.0	74	22	2	2
Subject 4					
7 December 1985	22.0	93	7	0	0
30 March 1988	10.6	81	13	2	0
8 March 1989					
RUL	8.1	91	6	3	0
Ling.	29.1	86	11	2	1

*After 1 week course of antibiotics

RML = Right middle lobe Ling. = Lingula RUL = Right upper lobe

Results of lavage repeated 3 or 4 times in 4 subjects are given in Table 4.5. Since the number of observations is small, meaningful inferences can not be made.

The mean fibronectin level in 10 non-smoking normal subjects was 6.31 + 1.83 (SD) μg/mg albumin. Fibronectin values more than two standard deviations above the mean of normal subjects i.e., >10 μm/mg albumin were classified as abnormally high. Fibronectin levels were estimated in 63 lavage samples. Results from 11 samples were excluded on technical ground. The remaining 52 samples were from 42 patients with 10 patients having 2 samples from 2 lavages. Twelve (28.6%) out of 42 patients had elevated fibronectin levels in BAL fluid. In 10 patients with repeat lavage, there was no significant difference in mean values of fibronectin levels (9) 1st lavage 11.5 + 7.8 vs 2nd lavage 14.1 + 12.9, $p>0.2$). Among these 10, four had elevated levels during 1st lavage and 3 continued to have elevated levels during 2nd lavage. One patient who had normal fibronectin during 1st lavage had an elevated level during 2nd lavage. Another subject with elevated level during 1st lavage had shown a reduction to normal value during 2nd lavage. Fibronectin is one of the toxic mediators released by activated alveolar macrophages, causing injury to the lung parenchyma[14].

Correlations of BAL Findings with Pulmonary Function and Severity of Exposure

Severity of exposure had negative correlations with FVC ($r = -0.297$, $p<0.05$) and $FEV_{1.0}$ ($r = -0.346$, $p<0.01$). However, severity of exposure had positive correlation with total cells ($r =$

0.551, $p<0.001$) and absolute alveolar macrophages ($r = 0.526$, $p<0.001$) from the lower respiratory tract.

$FEV_{1.0}$% had significant negative correlation with BAL neutrophil percentage ($r=-0.364$, $p<0.01$) and with absolute neutrophil count ($r=-0.304$, $p<0.05$). Similarly, $FEV_{1.0}$/FVC% had significant negative correlation with BAL neutrophil percentage ($r = -0.419$, $p<0.001$) and absolute neutrophils ($r= -0.333$, $p<0.01$).

The progression of macrophagic alveolitis to macrophage neutrophilic alveolitis with time and the observation of significant negative correlations of lower respiratory tract neutrophils to forced expiratory volume in one second and $FEV_{1.0}$/FVC% may suggest that cells comprising alveolitis especially neutrophils can cause deterioration in lung function. It had been reported that ventilatory function testing especially $FEV_{1.0}$ is a strong predictor of mortality in chronic obstructive pulmonary disease COPD[15]. The finding of significant negative correlation of BAL neutrophils with $FEV_{1.0}$ in this study warrants an intensive assessment and management of these patients with the available preventive and therapeutic modalities to prevent the sequelae of alveolitis on lung function. Effects of prolonged steroid therapy might have proved useful. The results of this investigation (BAL) have been published[16].

CONCLUSIONS

1. Macrophage – neutrophilic alveolitis was present in a proportion of severely exposed subjects evaluated 1-6 years after exposure.
2. The higher total cells in severely exposed smokers compared to non-smokers suggested that smoking was a risk factor.
3. Repeat lavage studies demonstrated that macrophagic alveolitis observed 1-3 years after exposure progressed to macrophage – neutrophilic alveolitis with time.
4. Fibronectin (one of the toxic mediators released by activated macrophages) levels were elevated in a proportion of patients. Elevated levels persisted in a proportion of patients on repeat lavage.
5. The observation of exaggerated number of alveolar macrophages and neutrophils in the lower respiratory tract along with abnormally elevated levels of fibronectin suggested that alveolitis in them might have caused further injury and fibrosis of lung parenchyma.
6. The finding of significant negative correlation of neutrophils with $FEV_{1.0}$ and $FEV_{1.0}$/FVC% further suggested that cells causing alveolitis especially neutrophils could have deleterious effects on lung function.

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Chapter 5

Respiratory Epidemiology of MIC/Toxic Gas Affected Population

Study Period : Mid-October 1985 to April 1988

1. To study the pattern of pulmonary disease emerging in the toxic gas exposed population.
2. To study the course of pulmonary disease over a period of time.

FIELD STUDIES

Sample Selection

Initially, a random sample of 5100 persons was selected from the gas exposed/affected population for respiratory epidemiological study and 2720 persons from this cohort were surveyed. Subsequently, it was decided to study respiratory morbidity from a fresh stratified random sample of 6106 subjects based on the criteria given in Table 5.1. This sample was provided from the cohort of the long term epidemiological study (Project 02) of the Indian Council of Medical Research (ICMR). Of the 2720 subjects studied from the initial cohort, 1816 persons were found to be common in both the cohorts and 904 did not have categorization. Thus, a sample of 7010 subjects was available for respiratory morbidity study. Number and coverage of subjects in each category are given in Table 5.2. A random sample of 2500 persons was also selected as controls from population who were not exposed to the toxic gas and also were comparable with regard to age, sex and socio-economic strata with the exposed population sample.

Table 5.1 Categorisation of Stratified Random Sample for Study

Category	Criteria (at time of inclusion)
I	Persons who were immediately affected and still suffering.
II	Persons who were immediately affected but were not suffering with respiratory symptoms at present
III	Persons who were immediately affected, became alright, developed respiratory symptoms later and were still suffering
IV	Immediately affected, became alright, developed respiratory symptoms later and became alright
V	No immediate effects, only later developed respiratory symptoms

Table 5.2 Coverage of Study Sample

Category	Sample	Coverage	%
I	1716	1190	69
II	1678	1097	65
III	0909	600	66
IV	1385	906	65
V	0326	166	51
VI	0092	75	82
Cases from first list, but not categorized	0904	0904	100
Total	7010	4938	70

Teams consisting of medical officer, field workers and laboratory technicians examined the exposed and control subjects in their homes as per standardized protocol that included administering a pre-structured respiratory questionnaire, physical examination, haemoglobin test, chest radiography and spirometry. A person was classified as drop-out if he/she could not be contacted after three home visits by a field worker. Thus, 4938 (70%) subjects from the exposed population and 1936 (77%) subjects from the control population were covered for study. In order to eliminate any bias in the survey, age, sex distribution, social status and severity of exposure of the covered and the uncovered samples were compared. No statistically significant difference was found in the two samples. The whole cohort covered under the study (n=4938) was categorized into three groups (severe, moderate and mild respectively) depending upon the severity of exposure according to the previously defined criteria (Tables 5.3 and 5.4).

Table 5.3 Criteria and Scoring Points of Severity of Exposure

	Criteria	Score
1	Area of exposure (ICMR designed) Mild : 11, 12, 13 Moderate : 3, 4, 5, 6, 9, 10 Severe : 1, 2 , 7, 8	 0.5 1 2
2	Death in family	2
3	Death in neighbourhood : (radius of 3 houses)	1
4	Hospitalisation in acute phase ICCU, Intensive care Regular admission	 3 2
5	Unconsciousness following exposure	2
6	Radiological evidence of pulmonary edema and/or patchy, nodular, reticular, reticulo-nodular opacities	2
7	Positive physical signs and/or linear opacities or increased bronchovascular markings	2
8	Pulmonary edema in family	1
9	Any two of following respiratory symptoms present continuously for at least 3 months after exposure : cough, dyspnoea, chest pain, inability to work.	1

Table 5.4 Classification of Sample on Basis of Severity of Exposure Score

Total score	**Severity of exposure**	**N**	**M**	**F**
0-8	Mild	557	239 (4.8)	318 (6.4)
8-10	Moderate	2304	1061 (21.5)	1243 (25.2)
≥10	Severe	2077	1044 (21.1)	1033 (20.9)
Total		4938	2344 (47.4)	2594 (52.5)

M = Males F = Female
Figures in parentheses indicate percentage of total

Pulmonary Function (Spirometry) Studies

Pulmonary function tests such as forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were performed using portable field spirometer (spirocheck). A minimum of three consistent readings were obtained on each subject and the highest value was used for analysis. The pulmonary function test results were compared with the predicted values derived from regression equations established for North Indian subjects. Pulmonary function test results were interpreted as per the criteria given in Table 5.5.

Table 5.5 Classification of Pulmonary Function Abnormalities

Normal	FVC > 80% predicted & FEV1/VC% > 80%
Obstruction cum restriction	FVC < 80% predicted & FEV1/VC% < 80%
Obstruction	FVC > 80% predicted & FEV1/VC% < 80%
Restriction	FVC < 80% predicted & FEV1/VC% >80%

Radiology

Each subject had skiagram chest PA view which was read by a panel of experts consisting of a physician and a radiologist. Ten percent of all the skiagrams were read by the Head of the Department of Radiology, All India Institute of Medical Sciences, New Delhi and the observations made by the expert panel were validated. The skiagrams were evaluated according to the modified International Labour Organisation (ILO) 1980 classification.

Table 5.6 Yearly Coverage of In-Depth Study Subjects

Category	Respiratory symptoms	Pulmonary function	Chest x-ray	Coverage	
				1988-89	-1990
I	Absent	Normal	Normal	55	54
II	Present	Normal	Normal	66	66
III	Present	Abnormal	Abnormal	66	63
IV	Present	Abnormal	Normal	49	45
V	Present	Normal	Abnormal	75	75
Total				311	303
Control				050	

IN-DEPTH STUDY

This study was started from May 1988. From the field study, a random sample of 311 subjects (Table 5.6) was selected for in-depth study that included detailed pulmonary function tests such as maximal expiratory flow rates and lung volumes. For the purpose of getting representative cases of varying degree and type of respiratory system involvement, cases from the field study were divided into five categories (Table 5.6) on the basis of acute phase respiratory symptomatogy, chest skiagrams and pulmonary function findings. Fifty unexposed subjects were also included as controls for comparison. All subjects were brought to the respiratory laboratory at Hamidia Hospital where clinical examination and detailed symptomatology were recorded in a pre-designed proforma. Pulmonary function tests were carried out using PK Morgan, Transfer Test Model C, U.K.

Routine blood and sputum examinations were done in all patients. Chest skiagrams were repeated yearly. Skin allergy testing was done in those who complained of breathlessness and whose pulmonary function showed airflow limitation, with bronchoreversibility. When there was improvement in the absolute value of FEV1 by more than 200ml, along with more than 15% improvement in FEV_1 and/or FVC and/or 30% improvement in forced mid-expiratory flow 25-75% (FMF 25-75%) following inhalation of a beta 2 stimulant, it was classified as significant bronchoreversibility. Patients having at least three of the following five criteria with normal FVC and FEV1 were diagnosed to have small airways obstruction.

1.	VEmax 50%	<75% predicted
2.	VEmax 75%	<75% predicted
3.	FMF 25-75%	<75% predicted
4.	RV/TLC ratio	>45%
5.	Difference between TLC and VA	500 ml

VEmax 50%, 75% = Maximal expiratory flow rates at 50% and 75% of FVC
VA = Alveolar volume during single breath diffusion test
TLC = Total lung capacity

Coverage of subjects in the in-depth study during 1988-89 and 1989-90 is given in Table 5.6. Subjective and objective scoring systems were developed in order to assess the overall outcome.

Subjective Scoring

Each symptom was given one mark if it was present in the baseline study or prior to gas exposure and zero mark if it was absent. During follow up the algebraic sum of the score was taken and if it was more than the baseline value it was considered as deterioration; if it was less than the baseline value it was taken as improvement; and if equal it was classified as stationary. If the score kept on changing it was then classified as fluctuating.

Objective Scoring

1. **Lung signs.** Same scoring pattern as in the case of subjective scoring was followed for lung signs.
2. **Pulmonary function.** In a normal population with increasing age, FEV1 does not decline till the age of 45 years and thereafter declines by 30 ml every year in non-smokers and upto 50 ml in smokers. In a given case, if the decline was 70 ml or more per year without significant bronchoreversibility, it was said to be deterioration (post bronchodilator value was used for comparison). If it remained in the expected limits, it was classified as stationary.
3. **Radiological.** Deterioration or improvement was judged depending on the extent of opacities in the follow-up x-ray films.

Overall assessment of the outcome was done as follows :

1 Improvement: subjective and objective improvement.

2 Deterioration: subjective deterioration and one objective parameter showing deterioration.

3 Stationary: no change in subjective or objective scoring.

4 Fluctuating: subjective fluctuation along with significant reversible airway obstruction.

Analysis of Data

Statistical analysis of data was done using ANOVA and students test.

RESULTS

Field Study

4938 subjects were covered out of a total cohort of 7010 thus, leaving 2072 (30%) dropouts.

Physical Characterisation

Age and sex distribution of the study population are provided in Table 5.7. The population covered in both the exposed and the control groups were mainly from the age groups 15-60 years. 2594 (53%) subjects of study population and 1144 (59%) of control population were females, 886 (18%) exposed subjects and 290 (15%) control subjects were smokers. The mean age, height, weight and hemoglobin concentration were comparable in exposed and control subjects (Table 5.8). Similarly, these parameters were similar in the severe, moderate and mildly exposed subjects (Table 5.8).

Table 5.7 Epidemiology Study Cohort : Age, Smoking, Habits and Severity of Exposure

Age (years)	Smoking habit	Severe		Moderate		Mild		Control	
		M	F	M	F	M	F	M	F
0-14	SM NS	001 287	000 224	000 260	001 271	000 056	000 046	001 265	000 220
15-40	SM NS	235 264	003 595	196 283	004 676	046 070	001 186	205 199	001 763
41-60	SM NS	140 075	000 171	151 106	003 237	029 025	003 065	063 033	001 136
> 60	SM NS	028 014	001 039	037 028	000 051	007 006	000 017	019 007	000 026
Total		1044	1033	1061	1243	239	318	792	1144

SM = Smoker NS = Non-smoker M = Male F = Female

Table 5.8 Physical Characteristics and Severity of Exposure (Mean ± SD)

Parameter		N	Severe	Moderate	Mild	Control
Age (Years)	M	951	29.00± 17.78	31.00± 20.26	32.00± 19.58	29.00± 17.18
	F	946	28.00± 17.71	29.00± 18.55	31.00± 18.47	27.00± 15.63
Height (cm)	M	941	148.00± 22.87	149.00± 20.46	148.00± 21.31	146.00± 26.54
	F	939	141.00± 20.45	141.00± 20.53	143.00± 15.71	142.00± 18.94
Weight (Kg)	M	941	43.00± 16.66	45.00± 16.78	46.00± 19.18	40.00± 16.24
	F	939	39.00± 15.12	41.00± 15.53	44.00± 15.55	39.00± 13.88
Hb (G%)	M	308	11.00± 02.76	11.00± 02.58	11.00± 03.18	11.00± 03.56
	F	332	10.00± 02.99	10.00± 02.76	11.00± 02.20	12.00± 02.49

Symptomatology

The symptomatology following the gas exposure is given in Tables 5.9 and 5.10. The main symptoms of exposed subjects were cough (98%) and dyspnoea (92%), whereas among control subjects, 19% had cough and 10% had dyspnoea. These symptoms were present in majority of patients irrespective of severity of exposure. Prolonged cough (more than 8

weeks) varied directly with severity of exposure (severe 48%, moderate 41%, and mild 29%, p<0.001). Similarly, the prevalence rates of muscular weakness, wheezing and disturbed consciousness were directly related to the severity of exposure (p<0.001). Naso-bronchial allergic manifestations were observed in a significantly large number of exposed patients compared to control subjects (p<0.001). However, it varied inversely with the severity of exposure (severe 9%, moderate 13%, mild 18% and controls 5%, p<0.005). There was no significant difference in the incidence of dermal allergy between exposed and control subjects.

Table 5.9 Symptomatology Following Toxic Gas Exposure

Symptom	**Severe (n=2077)**	**Moderate (n=2304)**	**Mild (n=537)**	**Total (n=4938)**	**Control (n=1936)**
Cough	2054 (98)	2259 (98)	543 (96)	4856 (98)	273 (19)
Expectoration	1358 (65)	1403 (61)	211 (38)	2972 (60)	165 (8)
Dyspnoea	1912 (92)	2152 (93)	491 (88)	4555 (92)	194 (10)
Wheezing	576 (28)	482 (21)	54 (10)	1112 (22)	60 (3)
Hemoptysis	102 (9)	102 (4)	30 (5)	234 (5)	12 (1)
Frothing	832 (40)	1036 (44)	209 (37)	2077 (42)	0
Muscle weakness	1615 (77)	1655 (71)	285 (51)	3555 (72)	3 (0.2)
Disturbed consciousness	442 (221)	361 (16)	39 (7)	842 (17)	0
Nasobronchial allergy	171 (9)	310 (13)	100 (18)	581 (12)	94 (5)
Dermal allergy	115 (6)	162 (7)	29 (5)	306 (6)	105 (5)

Table 5.10 Duration of Symptoms Following Toxic Gas Exposure

Symptom	**Toxic gas exposure**			
	Severe	**Moderate**	**Mild**	Total
Cough	N=2054	N=2259	N=0543	N=4856
<1 Week	195 (09)	314 (14)	123 (23)	632 (13)
1-2 Weeks	230 (12)	332 (15)	108 (20)	678 (14)
2-4 Weeks	287 (14)	292 (13)	48 (09)	627 (13)
4-8 Weeks	1988 (10)	188 (08)	50 (09)	436 (09)
Still continuing	993 (48)	920 (41)	162 (29)	2003 (43)
Information not Available	143 (07)	205 (09)	52 (10)	400 (08)
Expectoration	N=1358	N=1403	N=0211	N=2972
<1 Week	302 (22)	218 (16)	33 (16)	553 (19)
1-2 Weeks	137 (10)	213 (15)	38 (18)	388 (13)
2-4 Weeks	162 (12)	166 (12)	14 (07)	342 (12)
4-8 Weeks	172 (13)	120 (09)	18 (09)	310 (10)
>8 Weeks	150 (11)	233 (17)	19 (09)	402 (14)
Still continuing	435 (32)	453 (32)	89 (42)	977 (33)
Dyspnoea	N=1912	N=2152	N=0491	N=4555
<1 Week	405 (21)	454 (21)	103 (21)	962 (21)
1-2 Weeks	134 (07)	129 (06)	27 (05)	290 (06)
2-4 Weeks	100 (05)	109 (05)	11 (02)	220 (05)
4-8 Weeks	80 (04)	47 (02)	11 (02)	138 (03)
>8 Weeks	30 (02)	66 (03)	5 (01)	101 (02)
Still continuing	1163 (61)	1347 (63)	334 (68)	2844 (62)
Wheezing	N=0576	N=0482	N=0054	N=1112
<1 Week	483 (84)	365 (76)	34 (63)	882 (79)
>1 Week	93 (16)	117 (24)	20 (37)	230 (21)
Muscle weakness	N=1615	N=1655	N=0285	N=3555
<1 Week	385 (24)	271 (16)	41 (14)	697 (20)
1-4 Weeks	221 (14)	239 (14)	18 (06)	478 (13)
4-8 Weeks	128 (08)	76 (05)	11 (04)	215 (06)
Still continuing	881 (55)	1069 (65)	215 (75)	2165 (61)

Physical Signs

Ten percent of exposed subjects had rales and 8% had rhonchi (Table 5.11). The corresponding figures for control subjects were 4% and 2% respectively. The incidence of physical signs showed a declining trend as the severity of exposure diminished.

Table 5.11 Relationship of Lung Signs with Severity of Exposure

Signs	Severe (n=2077)	Moderate (n=2304)	Mild (n=0557)	Total (n=4938)	Control (n=1936)
Rales	269 (13)	194 (08)	33 (06)	496 (10)	78 (04)
Rhonchi	208 (10)	149 (06)	24 (04)	381 (08)	34 (02)

Figures in parentheses are percentages

Hospitalisation and Oxygen Therapy

Hospitalisation for respiratory problems was required in 30% of severely exposed, 15.5% of moderately and 4.5% of mildly exposed subjects and the difference was statistically significant ($p<0.001$, Table 5.12). Longer stay in hospital (more than one week) was needed in 10.5% severe, 4.5% moderate and 2.8% mild exposure subjects ($p<0.05$). Repeated hospitalizations for respiratory problems were required in significantly large number of cases from the exposed group compared with controls (Table 5.12). Clinical evidence of hypoxemia requiring oxygen therapy was present in 7.8% severely exposed, 2.9% moderately exposed and 1.4% mildly exposed subjects compared with controls (0.11%) ($p<0.02$).

Table 5.12 Relationship of Severity of Exposure with Hospitalization and Oxygen Therapy

Hospitalisation	N	Severe		Moderate		Mild		Control	
		M	F	M	F	M	F	M	F
		1044	1033	1061	1243	239	318	792	114
		308 (30)	306 (30)	168 (16)	191 (15)	007 (03)	016 (06)	001 (.1)	000 (00)
Duration									
<1 Week	N	194 (63)	192 (63)	112 (67)	131 (69)	003 (43)	006 (37)	000 -	000 -
1-2 Weeks	N	084 (27)	078 (23)	036 (21)	045 (24)	001 (14)	009 (56)	001 (.1)	000 -
3-4 Weeks	N	023 (7)	026 (8)	009 (5)	007 (4)	002 (29)	001 (6)	000 -	000 -
>4 Weeks	N	004 (1)	003 (1)	004 (2)	005 (3)	001 (14)	002 (12)	000 -	000 -
Information not available	N	3 (.1)	7 (2)	7 (4)	3 (1)	-	-	-	-
Re-hospitalisation	N	049 (05)	043 (04)	015 (01)	024 (02)	004 (02)	005 (02)	000 -	000 -
Oxygen therapy	N	088 (08)	073 (07)	032 (03)	036 (03)	004 (02)	004 (01)	001 (.1)	000 -

Figures in parentheses indicate percentages

Pulmonary Function Tests : Spirometry

The mean FVC and FEV1 were significantly lower in patients exposed to toxic gas (Table 5.13). Restrictive ventilatory defect was observed in 50% of exposed subjects. Obstructive ventilatory defect was seen in 7% and combined obstruction and restriction in 7% (Table 5.14). The corresponding figures in control subjects were 12%, 4% and 2% respectively. Pulmonary function abnormalities were more in severely and moderately exposed subjects

compared to mildly exposed subjects. Even in mildly exposed, the abnormalities were higher than those in control subjects. Thirty-six percent of exposed subjects and 82% of control subjects had normal spirometry test values.

Table 5.13 Pulmonary Function Results (Spirometry)

Parameters	Severe		Moderate		Mild	
	M 640	**F 1013**	**M 677**	**F 1217**	**M 157**	**F 317**
FVC (L)						
Observed	2.02* ± 0.53	1.66* ± 0.41	2.06* ± 0.58	1.66* ± 0.42	2.09* ± 0.51	1.76* ± 0.34
Predicted	2.83 ± 1.34	2.11 ± 0.75	2.89 ± 1.21	2.11 ± 0.73	2.81 ± 1.33	2.18 ± 0.61
FEV1 (L)						
Observed	1.81* ± 0.49	1.51* ± 0.42	1.84* ± 0.53	1.52* ± 0.42	1.90* ± 0.48	1.68* ± 0.40
Predicted	2.29 ± 1.05	1.75 ± 0.64	2.29 ± 0.94	1.74 ± 0.62	2.21 ± 1.05	1.79 ± 0.53
FEV1/FVC%	89.6 ± 09.2	91.0 ± 10.0	89.3 ± 09.1	91.6 ± 10.4	91.0 ± 09.4	95.0 ± 11.8

p<0.001, ** p<0.01

Table 5.14 Relationship of Pulmonary Function Abnormality with Severity of Exposure

Pulmonary function	**Exposure**				
	Severe 2054	**Moderate 2259**	**Mild 0557**	**Total 4870**	**Control 1936**
Restriction**	1036 (50)	1191 (53)	215 (38)	2442 (50)	232 (12)
Obstruction	150 (07)	178 (08)	24 (04)	352 (07)	85 (04)
Obstruction & Restriction	143 (07)	176 (08)	28 (05)	347 (07)	38 (02)
Normal**	725 (35)	714 (31)	290 (52)	1729(36)	1581 (82)

** See text for details

Radiology

Radiological findings were available in 1550 exposed and 835 control subjects (Table 5.15). 1095 (71%) of exposed and 704 (84%) of control subjects had normal chest skiagrams. The main radiological abnormalities observed in exposed people were interstitial lesions in 218 (14%) and peribronchial fibrosis in 79 (5%). Radiographic evidence of pulmonary tuberculosis was present in 100 (6%) patients. On comparison of radiology with pulmonary function status, it was observed that 54% of the patients with interstitial lesions had restrictive ventilatory defect (Table 5.16), 47% of patients with normal radiology had restriction, 56% of patients with peribronchial fibrosis had obstructive ventilatory defect and 38% of patients with normal radiology had obstruction. Twenty-eight percent of patients with interstitial lesions and 28% with peribronchial fibrosis had normal pulmonary function.

Table 5.15 Relationship of Radiological Features with Severity of Exposure

Radiological findings*	Severity of exposure			
	Severe (577)	**Moderate (792)**	**Mild (181)**	**Control (838)**
Normal	396 (68)	573 (73)	126 (69)	704 (84)
Pulmonary tuberculosis	41 (07)	48 (06)	11 (06)	17 (02)
Interstitial lesions	82 (14)	106 (13)	30 (17)	58 (07)
Peribronchial fibrosis	28 (05)	45 (06)	6 (03)	8 (.1)
Emphysema	6 (01)	5 (.6)	1 (.5)	3 (.3)
Large lesions	18 (03)	44 (06)	7 (04)	12 (01)
Discrete lesions	22 (04)	23 (03)	7 (04)	28 (03)

* Some patients had more than one type of abnormality

Table 5.16 Relationship of Radiological Features with Pulmonary Function

Pulmonary function status	Radiological features					
	Normal		**Interstitial lesions**		**Peribronchial fibrosis**	
	Exposed (n=1087)	**Control (n=704)**	**Exposed (n=218)**	**Control (n=58)**	**Exposed (n=79)**	Control (n=8)
Restriction	509 (47)	191 (27)	117 (54)	20 (4)	0	0
Obstruction & Restriction	064 (6)	012 (2)	29 (13)	2 (3)	13 (6)	0
Obstruction	034 (03)	025 (04)	12 (6)	3 (5)	44 (56)	2 (25)
Normal	480 (44)	476 (68)	60 (28)	33 (57)	22 (28)	6 (75)

Figures in parentheses are percentages

Clinical Diagnosis

Seventeen percent of exposed subjects had diagnosis suggestive of chronic bronchitis and this was based on symptomatology and pulmonary function. Twelve percent of subjects had features suggesting bronchial asthma and they did not have previous history of bronchial asthma or atopy. These subjects were classified as reactive airway dysfunction syndrome (RADS). Fifty-seven percent of patients with persistent respiratory symptoms who could not be classified into a known clinical entity were designated as unspecified lung disease (Table 5.17). The corresponding figures of chronic bronchitis, RADS and unspecified lung disease in control subjects were 7%, 5% and 0.2% respectively. By way of clarifying the true nature of symptoms, emphysema and pulmonary tuberculosis were detected in 0.2% and 2% respectively. Twelve percent were normal subjects classified as unspecified lung disease. A detailed evaluation including pulmonary function were done in a random sample of patients in the in-depth study (Ref : In-depth Study). Clinical diagnosis of pulmonary tuberculosis was made in 2% of exposed subjects and 1% of control subjects.

Table 5.17 Clinical Diagnosis and Severity of Exposure

Diagnosis	Exposure				
	Severe (n=2077)	**Moderate (n=2304)**	**Mild (n=0557)**	**Total (n=4938)**	**Control (n=1936)**
Unspecified lung disease	1327 (64)	1230 (53)	0264 (47)	2021 (57)	0003 (.2)
Chronic bronchitis	0335 (16)	0421 (18)	0079 (14)	835 (17)	0142 (07)
RADS/bronchial asthma	0171 (08)	0310 (13)	0100 (18)	0581 (12)	0094 (05)
Emphysema	0006 (.3)	0005 (.2)	0001 (.1)	0012 (.2)	0003 (.2)
Pulmonary tuberculosis	0041 (02)	0048 (02)	0011 (02)	0100 (02)	0017 (01)
Normal	0197 (09)	0290 (13)	0102 (18)	0589 (12)	1677 (86)

RADS: Reactive airways dysfunction syndrome

Table 5.18 Epidemiology Study, In-depth Study, Population Composition

Age group	Severe			Moderate			Control		
	Male		Female	Male		Female	Male		Female
	SM	NS	NS	SM	NS	NS	SM	NS	NS
<15	01	13	08	00	05	07	00	04	02
15-40	17	27	57	10	11	33	05	07	17
41-60	18	09	13	09	16	18	04	03	05
>60	04	05	03	01	01	02	02	00	01

SM – Smoker NS – Non-smoker

IN-DEPTH STUDY

Of the 311 subjects in the in-depth study, 288 were available for analysis. 175 of 288 subjects belonged to severely exposed and 113 to moderately exposed areas. Age and sex distribution and smoking habits are given in Table 5.18. 238 subjects (83%) belonged to the age group 15-60 years and 141 (49%) were females. Sixty of the 147 males (41%) were smokers.

Disease Pattern

Table 5.19 Disease Prevalence (n = 288)

Disease		Category									
		I		II		III		IV		V	
		NS	SM	NS	SM	NS	SM	NS	SM	NS	SM
CH.BR	S	01	01	06	07	05	03	10	02	07	02
	M	04	01	01	00	02	02	06	02	07	01
RADS	S	06	00	05	02	04	04	03	02	11	02
	M	02	00	07	01	08	03	01	00	08	01
BO	S	09	01	00	00	02	02	02	01	09	00
	M	02	00	04	01	02	00	00	00	01	02
RLD	S	00	00	01	00	00	00	02	01	00	00
	M	00	00	00	00	00	00	00	00	00	00
EMPHS	S	00	00	01	00	01	00	00	00	00	00
	M	00	00	00	00	00	01	00	00	00	00
B'CT	S	00	00	00	00	01	01	00	00	00	00
	M	00	00	00	00	00	00	00	00	00	00
P'TB	S	00	00	00	01	04	04	02	01	01	01
	M	00	00	01	00	03	01	00	00	04	01
NORM	S	14	01	15	00	05	00	03	01	05	00
	M	08	00	09	01	02	00	05	01	06	01
Total		46	04	50	13	39	29	34	1	59	11

NS = non-smoker, SM = smoker, CH.BR = chronic bronchitis
RADS = reactive airways dysfunction syndrome, EMPH = emphysema
BO = bronchiolitis obliterans, RLD = restrictive lung disease, EMPHS = emphysema,
B'CT = bronchiactasis, P'TB = pulmonary tuberculosis, NORM = normal
S = severely exposed area, M = moderately exposed area

Disease Suggestive of Chronic Bronchitis

Seventy subjects (24%) had persistent productive cough with or without airflow limitation and they were classified as chronic bronchitis. 44 patients belonged to severely exposed area and 26 to moderately exposed; 49 were non-smokers; 33 patients had persistent airflow limitation. Nineteen of these 33 patients were non-smokers. Even though the remaining 37 patients did not have airflow limitation, serial follow-up revealed significant annual decline

in FEV1 (more than 70 ml per year) in 7 subjects. Chronic bronchitis was observed in 4% of control subjects, but all of them were smokers (Table 5.20).

Table 5.20 Disease Prevalence in Control Population (n=50)

Disease	NS	SM
Chronic obstructive pulmonary disease	00	02
Bronchial asthma	01	00
Bronchiolitis obliterans	00	01
Restrictive lung disease	00	01
Pulmonary tuberculosis	03	00
Normal	35	07

Reactive Airways Dysfunction Syndrome (RADS)

Bronchial asthma – like features were seen in 70 patients (24%). Pulmonary function during acute attacks revealed reversible airways obstruction and the flow rates were normal in between attacks. Six subjects gave past/family history of bronchial asthma/atopy and had aggravation of symptoms following the gas exposure. Thus, 64 (22%) subjects without prior episodes of bronchial asthma had obstructive airways disease reversible with bronchodilators and were classified as "reactive airways dysfunction syndrome".

Small Airways Disease

In the field study, a large number of subjects who complained of exertional dyspnoea were classified as having restrictive ventilatory defect based on pulmonary function results obtained from "Spiro checks" and they were labelled as unspecified lung disease. However, on detailed pulmonary function testing, most of them were found to have significantly reduced FEF 25-75%, VEmax 50% and VEmax 75% with normal FVC and FEV1. These patients were classified as suffering from small airways disease. During in-depth study, it was observed that 38 patients (13.2%) had evidence of small airways obstruction. Thirty-one were non-smokers, radiological opacities such as reticular, reticulo-nodular and right paracardiac shadows were present in 16 of 38 patients, and hyperinflation in chest skiagrams in 5 cases.

Restrictive Lung Disease

Four patients had evidence of restrictive lung disease as evidenced by total lung capacity of less than 75% predicted; and all belonged to severely exposed area. All were below 33 years of age and had exertional dyspnoea and cough. Three of them were non-smokers. Two patients had retricular and reticulo-nodular opacities in right lower zone in chest skiagrams.

Pulmonary tuberculosis was found in 24 cases (8.3%) as against 6% in control population. Emphysema and bronchiectasis were diagnosed in three and two patients respectively. Two patients with emphysema were non-smokers and all three had increased total lung capacity and hyperinflation in chest skiagrams.

Course of Illness

Forty-six (16%) patients showed overall deterioration, 76 (27%) showed fluctuation, 32 (11%) had improvement and 110 (38%) were stationary. Twenty-four patients (8%) had pulmonary tuberculosis. Deterioration was more in severely exposed compared to moderately exposed population.

Table 5.21 Course of Illness (n = 288)

Disease		Category									
		I		II		III		IV		V	
		NS	SM	NS	SM	NS	SM	NS	SM	NS	SM
D	S	06	02	04	06	04	02	01	01	05	02
	M	02	01	02	01	01	03	00	00	02	01
F	S	06	00	08	02	04	04	03	02	11	02
	M	02	00	07	01	08	03	02	00	10	00
I	S	00	01	07	00	02	02	02	00	07	00
	M	00	00	04	01	00	00	03	00	02	01
NC	S	18	00	09	01	08	02	14	04	09	00
	M	12	00	08	00	05	00	07	03	08	02
P'TB	S	00	00	00	01	04	04	02	01	01	01
	M	00	00	01	00	03	01	00	00	04	01
Total		46	04	50	13	39	21	34	11	59	11

NS = non-smoker, SM = smoker, D = deterioration, I = improvement,
F = fluctuation, NC = no change, P'TB = pulmonary tuberculosis,
S = severe area, M = moderate area

Chapter 6

Long Term follow-Up Study Especially of Pulmonary Function in MIC/Toxic Gas Exposed Pateints

Study Period : December 1984 – December 1989

OBJECTIVES

To study the clinical profile of the toxic gas affected subjects by long term follow-up of clinical, radiological and pulmonary function parameters.

Two hundred fifty cases with definite history of exposure to toxic gas were selected from MIC ward and MIC out-patients of Hamidia Hospital, Bhopal. The registration of cases was done during the period December 1984 to December 1985 (Table 6.1). The patients were then classified into three groups (Severe, Moderate and Mild exposure) as per the criteria given in Table 5.3 of Chapter-5.

Table 6.1 Registration of Patients

Period of registration	Number of cases
0 – 2 months	61
2 – 4 months	52
4 – 6 months	85
6 – 8 months	33
8 – 10 months	19
Total	250

Clinical Profile

Detailed history of exposure, symptomatology, smoking habits, occupation, relevant illness history, personal and family history, and physical signs were recorded. Smoking history was noted with reference to type, quantity and duration in pack years. In the occupational history, it was noted whether it involved exposure to dust, fumes, pollutants, smoke, agriculture manure, pesticides etc. History of pre-exposure illness was recorded with reference to chronic bronchitis, recurrent chest infections, bronchial asthma, tuberculosis, allergic rhinitis, and eczema etc. The clinical status was recorded at each follow up with respect to both the presence or absence and change in severity of symptoms. Appearance of new symptoms was also noted.

Hematological investigations like hemoglobin estimation, total and differential leucocyte count, erythrocyte sedimentation rate (ESR) were done. Urine analysis for albumin, sugar and microscopic examinations were done. Sputum examinations for acid fast bacilli and culture sensitivity were also done in some cases.

Skiagrams of chest were done in all the cases initially and at subsequent follow ups. The x-rays were reported by a panel of experts which included clinician, radiologist and epidemiologist.

Pulmonary function measurements were initially done on Vitalograph portable spirometer (Cat. No. 21.100, Ireland). Subsequently, detailed lung function testing was done on computerized lung function test equipment (P.K.Morgan, UK) which included maximal expiratory flow rates, broncho-reversibility with salbutamol aerosol, lung volumes (helium dilution method) and single-breath carbon mono-oxide diffusion capacity. The values of various pulmonary function parameters were compared with predicted values derived from regression equations based on height, age and weight of Delhi population.

Blood gas analysis was done by BGM 1312 (Instrumentation Laboratory, USA). Arterial blood obtained by radial artery puncture was analysed for PH, PO2 and PCO2. Exercise tolerance test was performed on treadmill (S.N. 2063, P.K.Morgan, UK) to measure maximal oxygen uptake and exercise ventilation.

Calibration of all pulmonary equipments was done after every 15 tests and daily in cases of exercise treadmill and BGM. Accuracy tests and all quality control measures were done while performing various investigations.

Follow-Up

Follow-up of all the cases was done every year. A list of all the cases was prepared as per name, address, ICMR locality and follow up month. For the follow-up call, each case was visited personally by a field worker at least 3 times. Letter correspondence was done in migrated cases. During the follow up visits, the information regarding health status of the case, change of address and reasons of refusal were noted. In case of death at home or in other hospitals, information regarding cause of death was noted. Cases, who did not respond after 3 visits, were treated as defaulters and excluded from analysis. During each follow up, clinical status of the subjects was assessed and recorded on a computer format. Apart from various studies, all the cases were provided with treatment facility and hospitalization whenever required. The number of cases in subsequent follow ups are given in Table 6.2.

Till the end of the four year follow up, five patients died, 40 were untraceable and 37 defaulters.

Control Subjects

One hundred age, sex matched subjects were selected from the ICMR designated control area (14, 15, 16 locality) and their pulmonary functions were studied to compare with the exposed group.

Statistical Methods

All the data were presented as mean and standard deviation (S.D.). The results between exposed and control group were compared using the two tailed student t test. The changes in PFT values in the exposed group were analysed using “paired t test”.

Age and sex distributions of subjects are given in Table 6.3. One hundred sixty-eight subjects (67.2%) were males and 82 (32.8%) were females. Most of them (61%) belonged to the age group 15-40 years, 71 of 168 males (42%) were smokers. At the end of 5^{th} year, a total of 168 subjects were available for follow up, of which 113 (67%) were males (Table 6.4). Initially 141 subjects (56%) had severe exposure and at the end of follow up, 107 subjects (63.6%) were in the severely exposed category (Table 6.5).

Table 6.2 Follow-up of Patients

	Number of Cases
Baseline year (1985)	250 (100)
First year (1986)	210 (87)
Second year (1987)	201 (80)
Third year (1988)	191 (76)
Fourth year (1989)	168 (67)

Figures in parentheses are percentages

Table 6.3 Initial Distribution of Patients as per Age, Sex, & Smoking Habit (n = 250)

Age Group	Male		Female
	Smoker	Non-smoker	
Below 15 years	-	10	08
15 – 40 years	32	61	59
Above 40 years	39	26	15

Table 6.4 Distribution of Age, Sex, & Smoking Habit in Follow-up Cases (n = 168)

Age Group	Male		Female
	Smoker	Non-smoker	
Below 15 years	-	06	03
15 – 40 years	19	43	45
Above 40 years	27	18	07

Table 6.5 Distribution of Patients Based on Severity of Exposure

Severity of exposure	Initial Number (n=250)	Follow up (n=168)
Mild	40 (16)	26 (15.4)
Moderate	69 (28)	35 (21)
Severe	141 (56)	107 (63.6)

Symptomatology

Exertional dysponea was the commonest symptom (98%) initially and during follow up (Table 6.6). Chest pain, cough with or without expectoration and work intolerance improved for the initial one year followed by a stationary pattern in majority (70%) of cases. Frequency of chest infections decreased, although the incidence of cases with recurrent respiratory infections did not alter much.

Ophthalmic symptoms cured completely in 87% of cases within one year of exposure. Gastric symptoms were initially present in 133 (53%) cases; 67% of these showed complete recovery, whereas in 28%, symptoms persisted in less severe form. Incidence of impaired memory and concentration, joint pains and easy fatiguability increased in subsequent follow ups.

Table 6.6 Symptomatology (n = 250)

Symptoms	Number
Exertional dyspnoea	245 (98)
Recurrent chest infection	195 (78)
Easy fatiguability & work intolerance	132 (52.8)
Chest pain	105 (42)
Impaired memory & concentration	025 (10)
Joint pains	020 (08)

Figures in parentheses are percentages

Pre-exposure history of pulmonary tuberculosis was present in 4 (1.6%) which increased to 12 (4.7%) during subsequent follow-ups. Past history of bronchial asthma was present in 8 (3.2%), allergic rhinitis in 9 (3.6%) and chronic bronchitis in 6 (2.4%).

Routine hematological investigations did not reveal any significant abnormality except raised eosinophil count in 12.5% of cases.

Radiology

Retrospective analysis of skiagrams chest taken soon after the exposure revealed radiological evidence of pulmonary edema in 52 cases during acute episode. In the subsequent follow up; 66% of these developed streaky, retricular or reticulo-nodular opacities which were found to be progressive in 10 (19%) and stable in 42 cases. At the end of follow up, the common radiological abnormality was interstitial opacities (56%) i.e. linear, reticular, reticulo-nodular or paracardiac (Table 6.7). Active pulmonary tuberculosis was observed in 4.8% cases.

Radiological abnormalities showed increasing trend with severity of exposure (Table 6.7). Follow-up of radiological features revealed no significant change in majority (72%) - irrespective of severity of exposure (Table 6.8). Radiological deterioration (Table 6.9) was seen in 20% cases; of these 30% were smokers and 70% had severe exposure to toxic gas. Incidence of radiological deterioration increased with severity of exposure. Thirty-one percent of cases with interstitial opacities showed deterioration. The incidence of hyperinflation and prominent bronchovascular markings increased in subsequent follow-ups.

Table 6.7 Baseline Radiological Patterns in Toxic Gas Exposed Patients (n = 168)

Radiological pattern	No. of cases
Normal	20 (12)
Interstitial opacities	
Linear	16 (10)
Reticular	39 (23)
Reticulo-nodular	26 (15)
Paracardiac	13 (08)
Prominent bronchovascular markings	30 (18)
Emphysema and honey combing	06 (04)
Pulmonary tuberculosis*	09 (4.7)
Cardiac abnormality	09 (5.3)

Figures in parentheses are percentages

*Eight patients had active pulmonary tuberculosis

Table 6.8 Baseline Radiological Features with Respect to Severity of Exposure

Severity of exposure	Normal	BVM^+	Abnormal opacities	Others
Mild (n=26)	04 (16)	03 (11)	16 (62)	03 (11)
Moderate (n=35)	05 (14)	05 (14)	20 (58)	05 (14)
Severe (n=107)	11 (10)	22 (20)	58 (56)	16 (14)

BVM^+ : Increased bronchovascular markings

Figures in parentheses indicate percentages

Pulmonary Functions

Pulmonary function test results are given in Tables 6.10 and 6.11. Initial classification on the basis of conventional spirometry (Table 6.10) revealed abnormal pulmonary functions in 156 (62.4%) of cases which included obstruction in 49 (31%), restriction in 37 (24%) and combined obstruction and restriction in 70 (45%). Maximal expiratory flow rates at 50%, 75% and FEF 25-7% were found to be significantly low in exposed group ($p<0.0001$) as compared to controls; whereas values of RV/TLC ratio and TLC-VA difference were significantly high in exposed group ($p<0.001$).

Follow up studies of pulmonary function in 168 cases (Table 6.11) showed that there was a significant rise in FVC at 2nd year of follow up. Subsequently, there was no change in FVC. FEV1, TLC, and LCO did not show any change till the end of follow-up. However, residual volume had shown a gradual decline which was significant at 3rd year ($p<0.05$) and 4th year ($p<0.01$) of follow-up compared to baseline value. Annual decline in FEV1 was assessed in 123 cases with non-reactive stable airways (bronchoreversibility less than 10%). Significant decline (more than 50 ml/year) was observed in 24 (20%); of these 17(73%) were non-smokers, 50% had severe exposure and they included young as well as older age groups (39.4 ± 12.6).

Lung volumes were found to have a persistent decline in 11 cases, suggesting a progressive restriction. All the cases had interstitial opacities in skiagram chest. Only 4 cases showed decline in both FEV1 and lung volumes.

Table 6.9 Follow-up of Radiological Features in 168 Patients

Severity of exposure	Improved		Deteriorated		No change	
	N	%	N	%	N	%
Mild (n=26)	2	(8)	4	(15)	20	(77)
Moderate (n=35)	3	(8.5)	6	(17)	26	(74.5)
Severe (n=107)	7	(6)	24	(22)	76	(72)
Total	12	(8)	34	(20)	122	(72)

Table 6.10 Classification as per Baseline Pulmonary Function Tests

PFT group	FVC	FEV1	Initial (250)	Follow up (168)
Normal	>80% of pred.	>75% of pred.	94	67
Obstruction & restriction	<80% of pred.	<75% of pred.	70	44
Obstruction	>80% of pred.	<70% of pred.	49	32
Restriction	<80% of pred.	>75% of pred.	37	25

Table 6.11 Follow-up of Pulmonary Functions in 168 Cases

PFT Parameter	Baseline	I Year	II Year	III Year	IV Year
FVC (L)	2.73 ±0.9	2.91 ±0.81	2.98* ±0.83	2.98 ±0.80	2.95 ±0.84
FEV1 (L)	2.18 ±0.85	2.25 ±0.80	2.34 ±0.80	2.27 ±0.78	2.27 ±0.80
TLC (L)	4.77 ±0.92	4.82 ±0.95	4.82 ±0.93	4.70 ±0.91	4.60 ±0.97
RV (L)	1.82 ±0.56	1.76 ±0.56	1.77 ±0.59	1.71** ±0.58	1.65* ±0.57
DLCO (ml/min/mm Hg)	25.6 ±5.0	25.1 ±4.0	25.3 ±5.0	26.4 ±5.0	25.4 ±6.0

*p<0.01, **<0.05 compared to baseline

Table 6.12 Initial Survey of Arterial Acid Base Status (n=208)

Parameter	Value – Range	Incidence	%
PaO_2	< 40 mm Hg 60-80 mm Hg > 80 mm Hg	06 62 140	 30 67.2
$PaCO_2$	< 35 mm Hg 35-45 m Hg >45 mm Hg	31 172 05	14.8 82.8 2.4
PH	< 7.35 7.35-7.45 >7.45	07 197 04	3.5 94.5 2.0

Table 6.13 Oxygen Uptake and Dyspnoea Index in Baseline and Follow-up Studies and Comparison with Controls (n=50)

Parameter	Control	Exposed	Follow up
Oxygen uptake (ml/min - resting - VO_2 Max.	 270 ± 74 1905 ± 430	 239 ± 42* 1190 ± 306**	 233 ± 50 1330 ± 350*
Dyspnoea Index (Vemax/MVV)	36.3 ± 8.3	42.7 ± 10.8	39.4 ± 7.8

*p<0.05, **p<0.001

Arterial Blood Gases

Baseline study in 208 subjects revealed (Table 6.12) significant hypoxemia (PaO_2 less than 60 mm Hg) in only 6 (2.8%) cases; mild hypoxemia (PaO_2 60-80 mm Hg) in 62 (30%) while majority 140 (67.3%) had normal arterial oxygen tension. $PaCo_2$ was low (less than 35 mm Hg) in 31 (14.8%) and high (more than 45 mm Hg) in 5 cases (2.4%) who subsequently developed corpulmonale.

Follow-up study in150 cases did not reveal any significant change in the acid base status of the exposed population.

Exercise Tolerance Test

Exercise tolerance test was initially done in 50 gas exposed symptomatic cases and compared with 50 age, sex matched controls. Oxygen uptake at rest and maximum oxygen uptake (VO_2Max) were significantly low in exposed group (Table 6.13). Dyspnoeic index (VEMax/MVV) was found to be marginally elevated in exposed group.

Disease Patterns

1. **Obstructive airways disease.** At least 20% cases developed obstructive airways disease as suggested by clinical and radiological assessment. These patients on follow-up had persistent irreversible airway obstruction with significant annual decline in FEV1 and hypoxemia.
2. **Reactive airway dysfunction syndrome.** Twelve percent cases from this cohort developed features suggestive of bronchial asthma, without having any pre exposure history of bronchial asthma or atopy.
3. **Restrictive lung disease.** Exertional dyspnoea, radiological opacities and reduced lung volumes were observed in 15 cases (6%).
4. **Small airways disease.** A substantial number of subjects had features suggestive of small airways disease as evidenced by significantly reduced expiratory flow rates at 50% and 75% of vital capacity.

Sequelae

1. **Cor pulmonale and respiratory failure.** Five cases who developed COPD after exposure, later showed clinical evidence of pulmonary hypertension and right sided failure, supported by x-ray and ECG findings and raised CO_2 levels in arterial blood gas study. Three of these cases died later in spite of vigorous treatment.
2. **Recurrent respiratory infections.** Many cases showed evidence of recurrent chest infections.

3. **Interstitial lung disease.** Clinical, radiological and pulmonary function tests revealed that alveolar fibrosis could occur in some cases which appear to be non-progressive at present.

DISCUSSION (Chapters 5 and 6)

Respiratory epidemiological and hospital based long term studies have revealed that respiratory symptoms such as cough, and dyspnoea were persisting in a large number of subjects (92-98%) following exposure to the toxic gas. In addition, a good proportion of subjects had muscular weakness. A significantly large number of subjects especially those with severe exposure required repeated hospitalization for their respiratory ailment. Pulmonary functions were significantly lower in exposed subjects and continued to be significantly lower in follow up. Follow up studies of PFT demonstrated that FVC improved significantly during 2^{nd} year follow up, subsequently there was a stable course. FEV1, TLC and LCO showed a stable course throughout the follow-up. However, there was a significant reduction in residual volume at 5^{th} year compared to initial value. The main types of pulmonary function abnormalities noticed were airflow limitation. Both irreversible and reversible airflow limitation was seen in a substantial number of subjects. Isolated airflow limitation in small airways also seen in a proportion of subjects. Restrictive ventilatory defect was seen in a small proportion of patients.

The main radiological abnormalities were interstitial lesions that included streaky, reticular and reticulo-nodular opacities. Another important radiological finding was peribronchial fibrosis. A substantial number of subjects (71%) had normal chest x-rays. Radiological abnormalities were higher in severely exposed subjects and there was no significant change in abnormality during follow-up.

These studies had demonstrated that 20% of subjects had features suggestive of chronic bronchitis that included persistent cough with or without irreversible airflow limitation. Twelve percent of subjects had features suggestive of bronchial asthma. These patients had reversible airflow obstruction and a fluctuating course of disease responding to bronchodilators. Most of these patients did not have previous history of bronchial asthma or atopy. Small airways disease as evidenced by significantly reduced flow rates in PEF 25-75%, VEMax 50% and VEMax 75% was seen in 13% of subjects, having normal in FVC and FEV_1. Most of them were non-smokers. They had symptoms of cough and exertional dyspnoea and radiological features of interstitial lesions. Alveolar fibrosis resulting in reduced lung volumes was found in 2 to 5% of subjects. The significantly reduced residual volume at 5^{th} year of follow up also suggests the possibility of reduction of alveolar air trapping, or alveolar fibrosis, following the toxic gas exposure. These patients complained of cough, dyspnoea and had interstitial lesions in chest x-rays. Chronic cor pulmonale, respiratory failure and recurrent respiratory infections were important sequelae that observed in these patients.

Chapter 7

Disproportionate Symptoms In MIC/Toxic Gas Exposed Population, Pulmonary Function Tests, Blood Gases and Urinary Thiocyanate Excretion

Study Period : 1985 to 1990

INTRODUCTION

Inhalation of MIC/toxic gas in Bhopal Gas Disaster, in 99% of the exposees, produced cough, respiratory distress, tachypnoea, chest pain and loss of work capacity. These clinical manifestations in many cases were considered disproportionate in that; these were poorly correlated with clinical history and findings, chest radiograph, pulmonary function tests and arterial blood gases. Furthermore, response to conventional respiratory therapy with antibiotics, bronchodilators, corticosteroids and cough suppressants proved inadequate, while these symptoms persisted or recurred over extended periods of time.

The studies presented in this chapter were planned to understand the mechanisms underlying the respiratory symptoms and also to try modalities of treatment which would ameliorate them. These studies were carried out at the Jawahar Lal Nehru Hospital (JNH) in Bhopal on patients selected from the toxic gas exposed population as well as from the unexposed population to act as "normal controls" for comparison. The study period lasted from 1985 to 1990.

All investigations on sample drawn from exposed population compared with sample drawn from unexposed or control population were aimed at : (1) effect on oxygen transport in the body and its utilization by tissues by estimation of Hb and its N-carbamoylation, measurement of arterial and venous blood gases, blood levels of 2-3 diphosphoglycerate (DPG); (2) assessment of cyanide pool (evidence of cyanide poisoning) in the body by measurement of urinary thiocyanate excretion before and after provocative dose of NaTS; (3) evaluation of chest radiographs and assessment of pulmonary function status; and (4) evaluating response to therapeutic modalities like administration of NaTS, broncho-dilators etc.

The entire study is presented here in two parts : (i) covering the period from 1985 to 1986; (ii) Long term ICMR cohort study frorm 1987 to 1990.

Part I - (1985 – 1986)
Oxygen Transport and Utilisation by Tissues

1. **Haemoglobin (Hb).** Sixteen adults, age range 16-47, 9 males, 7 females, and 4 children who were severely exposed to toxic gas were taken up for investigation. Most of them had severe symptoms with respiratory distress and tachypnoea, loss of work capacity, and tachycardia. Two of the 4 children had almost complete loss of appetite and showed evidence of malnutrition. All patients came from very poor socio-economic strata. Twelve of the twenty patients had haemoglobin concentration of more than 12 G%. In another restrospective study, out of 120 blood samples 86 patients had more than 12 G% Hb.

2. **Carbamoylation of Hb.** There is unequivocal evidence that on entering the blood MIC caused irreversible N-carbamoylation of end terminal valine residues of Hb1,2. Depending on the number of Hb chains affected, the transport of CO2 would be impaired, with consequent higher affinity for oxygen in the toxic gas exposed patients. This partly explained the red discoloration of blood in them. More importantly, the resultant diminished unloading of oxygen in the tissues could also cause tissue anoxia. This provides suggestive evidence that the toxic gas had crossed the pulmonary barrier.

3. **2-3 Diphosphoglycerate (DPG).** Twenty-eight venous blood samples were tested for 2-3 DPG levels with phosphoglucomutase enzyme technique (Normal values = 1.0 to 2.15 n moles per ml, mean 1.45 ± 0.135 nmoles). Twenty-five of these samples showed values higher than 2.5 n moles. This finding was suggestive of oxygen lack, and was similar to that found in Indian soldiers exposed to high altitudes, above 14,000 feet for 2 weeks. The values returned to normal levels by July 1986. Sixteen maternal cord blood samples of toxic gas exposed women showed normal 2-3 DPG values in 6 cases and above 1.5 n moles in 10 cases. Only 2 out of 16 cord blood samples showed elevated levels.

4. **Arterial and venous blood gases**. Arterial blood gases in the immediate post-exposure period were measured with Radiometer electrodes. In 13 patients PaO2 ranged between 60 to 80.5 mmHg; in the remaining two patients the values were less than 60 mmHg. The PaCO2 values ranged between 26.6 to 44.8 mmHg. Peripheral venous blood in 10 out of 18 patients showed PCO2 ranging between 45 to 70 mmHg. In all patients, mixed venous blood collected by right heart catheterization showed PCO2 values not significantly different from peripheral venous blood.

In another study at a later date, 36 out of 45 patients showed PaCO2 values less than 40 mm Hg. The blood gas data analysed in the light of relatively normal pulmonary function test values did not explain the symptom of breathlessness/respiratory distress.

Assessment of Cyanide Pool

High levels of cyanide were found in blood and in the post-mortem tissues of persons who died between 3 and 6 December, 1984. This provided convincing evidence that HCN was also one of the constituents of the gases generated as a result of pyrolation of MIC. Thus, cherry red discoloration of blood and viscera on autopsy could be explained. The role of HCN in the toxic gas exposed population was investigated by determining urinary excretion of thiocyanate before and after intravenous administration of NaTS.

Rationale of Treatment with Sodium Thiosulphate (NaTS)

Methyl isocyanate itself, though an organic compound, on inhalation could have diffused into the tissues along with other gaseous products and carbamoylated Hb irreversibly. These products might include compounds (HCN etc.) needing sulphate donors for detoxification. The toxic gases also could have caused reversible carbamoylation leading to possible delayed effects due to late release of the gas products from carbamoylated proteins of the body over the following days and months.

Based on the above hypothesis, it was decided to conduct a therapeutic trial with i/v NaTS in patients who continued to be seriously ill for more than 6 weeks despite the intensive

conventional treatment and who had consented to undergo this trial therapy of their free will. Ten millilitre of 10% NaTS was administered i/v. This dose was considered adequate, 4-6 weeks after the gas exposure.

Results of Clinical Trials (January – February 1985)

A total of twenty patients underwent this trial treatment. Twelve of them showed remarkable clinical improvement in respiratory symptoms. However, mild to moderate tachycardia on exertion persisted. Six of the twenty patients clinically improved but required continuation of treatment for residual persistent though not disabling symptoms. The remaining two patients showed no clinical improvement.

Based on the results of this pilot study, another group of 50 patients with severe respiratory symptoms were treated with NaTS. The symptoms of cough, breathlessness, easy fatigability and loss of work capacity were ameliorated. However, symptoms which did not improve were : burning sensation in epigastrium, vague muscle and joint pains, loss of memory and black spots in vision.

During the years 1985 – 1986, 230 patients were administered 1000 injections of NaTS. The following side effects were noted : feverishness – 5, loss of memory –1, exaggerated reflexes – 1, sensation of body heat – 1, skin rash – 1, venospasm – 1. Five patients who were assessed as 'cured', had recurrence of symptoms after 2 to 7 weeks, viz., respiratory symptoms and loss of work capacity. Four of these patients who agreed for blood gas analysis showed reduction in PVCO2. On administration of 1 to 4 injections of NaTS, they showed increase in PVCO2 pari passu with complete relief of symptoms.

Urinary Thiocyanate Excretion

A double blind controlled trial of i/v NaTS in gas exposed patients showed the following results:

1. Majority of the patients excreted much higher than normal concentration of thiocyanate in the urine.
2. Administration of NaTS produced significant increase in the excretion of thiocyanate – maximum being approximately 5 hour after the injection.
3. After six injections of NaTS the excretion of thiocyanate stabilised.
4. Despite subjective improvement in respiratory symptoms the respiratory rate did not show any significant change.
5. The 12 hour excretion of thiocyanate following a single or three injections of NaTS did not show any significant difference.

Clinical Trial of NaTS at Jawahar Lal Nehru Hospital (JNH)

A retrospective analysis of data of NaTS trial at the JNH Hospital during May to December 1985 regarding effect on recurrent respiratory problems in the paediatric age group of 6 to 12 years was done. The clinical history, symptoms and the effect of treatment were documented from the statement of the mother. The patients getting treatment with other drugs were excluded from the study. The effect of i/v NaTS on random urine samples was also assessed simultaneously.

Fifty patients in the following age groups were included in the study : < 2 years –4, >2 <5 – 10, >5 <10 – 27, and ≥10 – 9. The toxic gas exposure was assessed as : mild – 4, moderate – 29, and severe – 17.

Relief of Symptoms. Thirty-six out of the 50 patients got 50-100% relief of symptoms. Thirty-five patients showed a significant fall in urinary thiocyanate excretion while one patient showed no change. Six of the 50 patients showed approximately 25% relief of symptoms; five of them showed a corresponding fall in the urinary thiocyanate excretion, in one patient the level actually rose. Six patients obtained no relief in symptoms. The relevant data on the remaining two patients was inadequate to be analysed. Symptoms recurred in nine patients. On recurrence of symptoms the patients received only NaTS. Pretreatment urinary thiocyanate in 5 out of nine patients was less than 1.0 mg%. When symptoms recurred urinary thiocyanates also increased to >1 mg%.

It was observed that even six months after the gas exposure the patients benefitted from NaTS, including those with relapsing symptoms. Recurrence of symptoms in a minority of the "cured patients" and the ensuing relief after taking NaTS again strongly suggests that MIC and its breakdown products had entered the blood stream and tissues and were possibly releasing toxic breakdown products in the body which affected the Hb, and oxygen utilization, *etc.* and which could be only removed as urinary thiocyanate by using a sulphane donor such as NaTS. It may be concluded that urinary thiocyanate excretion level reflected directly the patient's clinical status, well-being or recurrence of illness.

Part II – Long Term ICMR Cohort Study (1987 – 1990)

Patients for long term studies were selected from the ICMR cohort for epidemiological studies.

Selection of Study Material

- The patient was residing in the severely exposed area at the time of gas leak.
- There was at least one death in the family after the exposure.
- Symptoms were severe enough for prolonged hospitalization.

After a thorough clinical history and examination, blood was tested for cell counts, ABG analysis, 2,3 DPG, urinary thiocyanate estimation, pulmonary function tests and chest radiograph. The latter were interpreted according to standard procedure by an expert group appointed by the ICMR. It was also decided to continue NaTS study. Injection of NaTS was given daily for 6 days after explaining all the dietary precautions to the patient. Urinary thiocyanate estimation was repeated on 6^{th} day along with recording of clinical symptoms and findings on physical examination.

Urinary Thiocyanate Excretion Study

The data on serial studies of urinary thiocyanate excretion in the severely exposed group (September 1987 to November 1990) are presented in Tables 7.1 to 7.5. It can be seen that there was gradual lowering of urinary thiocanate levels to less than 1 mg% in 1987-88 compared with previous years. The results of the paired 't' test indicate that there is no significant trend seen in 1988-89, meaning that the conditions had more or less stabilised. On applying the 't' test on various groups based on age, sex, smoking habits, no significant intragroup difference was seen.

Table 7.1 Urinary Thiocyanate Levels in Spot Samples (September 1987 to November 1990)

Year	Total	More than 1 mg (%)	Less than 1 mg (%)
1986-87	133	70.60	29.40
1987-88	274	20.81	79.19
1988-89	256	20.70	79.30
1989-90	152	19.08	80.92

Table 7.2 Paired 't' Test on Age/Sex Based Groups

	Group	n	Values of urinary thiocyanate in		't'	Significance
			1985-86	1987-88		
A	Below 40 years: Males	44	Mean – 1.2354 S.D. ± 0.4554	Mean – 0.8931 S.D. ± 0.4054	4.5197	99 Significant
B	Below 40 years: Females	41	Mean – 1.2178 S.D. ± 0.5446	Mean – 0.7066 S.D. ± 0.817	5.4916	99 Significant
C	Above 40 years: Males	36	Mean – 1.2708 S.D. ± 0.7574	Mean – 0.8229 S.D. ± 0.3755	3.0	Significant
D	Above 40 years: Females	12	Mean – 1.0341 S.D. ± 0.4508	Mean – 0.7166 S.D. ± 0.2525	2.0631	Insignificant

Table 7.3 Paired 't' Test on Age/Sex Based Groups

	Group	n	Values of urinary thiocyanate in		't'	Significance
			1987-88	1988-89		
A	Below 40 years: Males	44	Mean – 0.8931 S.D. ± 0.4054	Mean – 0.8833 S.D. ± 0.3948	0.0213	Not significant
B	Below 40 years: Females	41	Mean – 0.7066 S.D. ± 0.3817	Mean – 0.7768 S.D. ± 0.3090	0.9141	Not significant
C	Above 40 years: Males	36	Mean – 0.8229 S.D. ± 0.3755	Mean – 0.7431 S.D. ± 0.3567	0.9223	Not significant
D	Above 40 years: Females	12	Mean – 0.7166 S.D. ± 0.2525	Mean – 0.7625 S.D. ± 0.2694	0.4305	Not significant

Table 7.4 Paired 't' Test on Groups Based on Urinary Thiocyanate Values

Group	N	Values of urinary thiocyanate in		't'	Significance
		1985-86	1987-88		
Previous values of more than 1 mg%	88	Mean – 1.4538 S.D. ± 0.3760	Mean – 0.8364 S.D. ± 0.4040	11.2143	Highly significant
Previous values of less than 1 mg%	45	Mean – 0.6627	Mean – 0.7134	0.1929	Not significant

Table 7.5 Paired 't' Test on Groups Based on Urinary Thiocyanate Values

Group	n	Values of urinary thiocyanate in		't'	Significance
		1987-88	1988-89		
Previous values (1985-86) of more than 1 mg%	88	Mean – 0.8364 S.D. ± 0.4040	Mean – 0.7984 S.D. ± 0.3515	0.655	Not significant
Previous values (1985-86) of less than 1 mg%	45	Mean – 0.7134 S.D. ± 0.3549	Mean – 0.6944 S.D. ± 0.2935	0.2770	Not significant

Pulmonary Function Studies

Pulmonary function test data are given in tables 7.6, 7.7. It can be seen that in 1986-87, 93% of the patients had abnormal lung function, and only 7% were normal. In 1989-90, 71% of them continued to be abnormal while 29% had become normal. Over the years there was also shift from restrictive to restrictive-cum-obstructive pulmonary impairment.

Many patients of the cohort developed bronchial asthma like picture. They started getting recurrent attacks of breathlessness following the exposure to toxic gas. Out of these, 107 of the patients showed good response to bronchodilator i.e. metered dose of salbutamol aerosol. Out of this group, 70% of the patients had no previous history of bronchial asthma.

Table 7.6 Comparative Study of Pulmonary Function Tests Done Over the Last Four Years

Year	n	Normal (%)	Abnormal (%)	Obstructive (%)	Restrictive (%)	Obst.-cum-restrictive (%)
1986-87	245	07.00	93.00	-	-	-
1987-88	269	17.10	82.88	25.27	39.03	18.58
1988-89	272	28.70	71.16	22.09	19.24	29.96
1989-90	260	29.00	71.00	26.00	25.00	20.00

Table 7.7 Comparison of PFT for Depicting Deterioration/Improvement (More than 15% change over the period of last 4 years)

	1987-88 n = 269	1988-89 n = 272	1989-90 n = 260
Same status	34.1% (83)	76.80% (209)	73.08% (190)
Improvement	15.44% (38)	10.66% (29)	10.77% (28)
Deterioration	50.4% (124)	12.53% (34)	16.2% (42)

Figures in parentheses indicate number of patients

Comparison of pulmonary function test values over the years in these patients showed that in 1989-90, 190 (73.08%) patients did not show any significant change in their lung function; 42 (16.2%) patients showed deterioration with more than 15% change in their lung function test parameters; 26 (10.8%) patients showed improvement. Twenty-eight patients of this group had shown deterioration of lung function in the previous year also. Most of these patients were developing chronic obstructive airway disease only. Twenty-eight (10.77%) patients improved after initial decline. Six patients showed persistant decline in their lung volumes (RV, TLC, DLCO) over the years.

Response to Bronchodilators

Those patients who showed obstructive changes in their lung function were administered 500 mcg salbutamol aerosol inhalation. Their pulmonary function tests were repeated 10 minutes after inhalation. In the year 1989-90, 102 patients were subjected to the test. It was found that 29% of patients showed no change in their lung function values whereas 71% of patients showed more than 15% change in their lung function values. The percentage of patients with significant reversibility increased from 50% to 71%.

X-Ray Chest Study

In the follow-up study of chest radiographs, these were evaluated by the expert group of three formed by ICMR. These were randomly mixed with that of control group which constituted around 30%.

1987-88

Total x-rays done	187
Good x-rays	151
Under exposed/over exposed	36

The results of the evaluation of chest radiographs are given in Tables 7.8 and 7.9.

Table 7.8 PA X-ray Chest Findings in Toxic Gas Exposed Compared with Unexposed Control Population

Parameter	Study period			
	1987-88		1988-89	
Population	**Exposed**	**Control**	**Exposed**	**Control**
Number	151	103	172	103
X-ray Findings No abnormality	96 (63.5%)	77 (74.8%)	79 (45.9%)	77 (74.8%)
Pericardiac/peribronchial fibrosis	19 (12.5%)	4 (3.9%)	40 (23.2%)	4 (3.9%)
Reticulo-micro nodular opacities	17 (11.2%)	9 (8.7%)	46 (26.7%)	9 (8.7%)
Honey combing	9 (5.9%)	-	14 (8.1%)	-
Tuberculosis	5 (3.3%)	4 (3.9%)	7 (4.0%)	4 (3.9%)
Hilar shadows	17 (11.2%)	9 (8.8%)	35 (20.3%)	9 (8.7%)
Emphysema	-	1 (1.0%)	-	1 (1.0%)
Diffuse interstitial fibrosis	6 (3.9%)	-	4 (2.3%)	-

Table 7.9 PA X-ray Chest Findings in Toxic Gas Exposed Smokers Compared with Unexposed Control Smokers

Parameter	Study period			
	1987-88		1988-89	
Population	**Exposed**	**Control**	**Exposed**	**Control**
Number of smokers and ex-smokers	35	26	42	26
X-ray Findings No abnormality	17 (48.6%)	17 (65.4%)	17 (40.5%)	17 (65.4%)
Pericardiac/peribronchial fibrosis	8 (22.9%)	3 (11.5%)	13 (30.9%)	3 (11.5%)
Reticulo-micro nodular opacities	6 (17.1%)	3 (11.5%)	16 (50.0%)	3 (11.5%)
Honey combing	4 (11.5%)	-	6 (14.3%)	-
Tuberculosis	1 (0.3%)	2 (7.7%)	1 (2.4%)	2 (7.7%)
Hilar shadows	4 (11.5%)	2 (7.7%)	7 (16.7%)	2 (7.7%)
Emphysema	-	1 (3.9%)	-	11 (3.9%)
Diffuse interstitial fibrosis	3 (8.6%)	-	1 (1.4%)	-

Detailed analysis of 151 chest x-rays of patients of the cohort showed that in 1987-88, 36.42% of x-rays were abnormal, while in 1988-89, 55% were abnormal. On follow-up of these chest skiagrams a year later 17.2% x-rays showed evidence of deterioration. Tables 7.8 and 7.9 show that in 1987-88 interstitial opacities, i.e., linear, reticulonodular, paracardic and peribronchial were the commonest and comprised 24.7% of abnormal x-rays. Their frequency increased to 48% in the year 1988-89. Pulmonary tuberculosis was seen in 4.0% of cases which improved after treatment. Prominent hilar shadows incidence increased from 11.0% to 20.0% in the year 1988-89. It can be further seen that x-ray abnormalities were more common in smokers and ex-smokers when compared with non-smokers.

An effort was made to match x-rays with PFTs and it was found that there was mismatch of 41.0% in 1987-88 and 31.8% in 1988-89. This decrease in the mismatch is probably due to further deterioration in x-ray findings and pulmonary functions.

Table 7.10 Comparison of Chest X-rays and PFT in 1987-88

Group	PFT/Chest skiagram	Number	
I	Normal x-ray and normal PFT	48	
II	Abnormal x-ray and abnormal PFT	30	59%
III	Abnormal x-ray and normal PFT	12	
IV	Normal x-ray and abnormal PFT	42	41%
Total		132	

Tables 7.10 to 7.13 show that there was significant association between PFT values and chest skiagram ($p<0.05$). Comparison of group III, i.e., abnormal chest skiagram with normal pulmonary functions was seen in 12 persons in 1987-88 and in 25 in 1988-89.

Comparison of group IV in 1987-88, i.e., normal x-ray chest with abnormal pulmonary function showed obstructive pattern in 18 (42.8) out of 42, the rest showed restrictive and mixed pattern.

Table 7.11 Group Criteria for PFT and Chest Skiagrams in 1988-89

Group	PFT/Chest skiagram	Number	
I	Normal x-ray and normal PFT	67	
II	Abnormal x-ray and abnormal PFT	48	69%
III	Abnormal x-ray and normal PFT	25	
IV	Normal x-ray and abnormal PFT	27	31%
Total		167	

Comparison in the same way was done in group IV for 1988-89. Results showed that out of 27 persons having normal x-rays, 15 (55%) had obstructive pattern on PFT and the rest had restrictive and mixed pattern.

Table 7.12 Normal X-ray/Abnormal PFT in 1988-89

Obstructive	15	55.56%
Restrictive	5	18.52%
Obstructive-cum-restrictive	7	25.92%

Table 7.13 Average PFT Values in Restrictive and Restrictive-cum-Obstructive Groups

Groups	FVC	FEV_1	FEV_1/FVC
Restrictive	61%	52%	95%
Restrictive-cum-obstructive	78%	87%	108%

Blood Gas Analysis

Arterial blood gas values in 257 patients during the year 1987-88 showed no significant changes in 1988-1989. In 123 patients $PVCO_2$ when compared with 1984-85, 1985-86 values showed significant downward trend. In 1984-85 more than 70.0% showed high $PVCO_2$, whereas in 1987-88 only 20.0% of patients were hyperventilating.

Follow-Up

During follow-up period of the study, 20 patients died: 1986-87 (4), 1987-88 (3), 1988-89 (8), 1989-90 (5). Seven of them were smokers, whereas 13 were non-smokers. Cause of death was cor pulmonale with CCF in 9 patients. All of them died in hospital, were either admitted in the hospital or were brought just before their death. Three of them died due to various other ailments; bronchogenic carcinoma (1), myocardial infarction (1) and unknown cause (1).

CONCLUSIONS

1. MIC/toxic gas crossed the alveolar-capillary barrier and entered systemic circulation as evident by high Hb%, N-Carbamoylation and high urinary thiocyanate levels.
2. Intense weakness in patients was because of poor O2 utilisation in end organs, which improved after giving sodium thiosulphate injections.
3. There was damage to CO2 transport mechanism in the haemoglobin due to carbamoylation of free terminal aminogroups of haemoglobin.
4. Exposure to single high dose of MIC/toxic gas resulted in bronchial asthma like picture, not amenable to conventional drug therapy.
5. Many patients showed persistent deterioration resulting in chronic airways disease, leading to corpulmonale.
6. Symptomatic patients with no evidence of objective abnormalities should be further evaluated to find out the cause of illness and proper management.

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Chapter - 8

Sequential Respiratory, Psychologic and Immunologic Studies in Relation to MIC/Toxic Gas Over Two Years

INTRODUCTION

The Railway Colony of Bhopal inhabited by approximately 10000 people is located within 0.5 to 1.0 km of the Union Carbide Factory. All residents were severely exposed to methyl isocyanate (MIC)/ toxic gas. One hundred thirty five people died within 4 weeks of the exposure, 1640 subjects had been treated by doctors and 872 were hospitalized for treatment.

In order to study sequential behaviour of toxic gas exposed and persistently symptomatic subjects a cohort of 113 subjects were regularly followed upto 2 years. The initial study results are published[1,2]. The present communication presents in detail the results of sequential respiratory, psychologic and immunologic studies.

One hundred thirteen subjects, from a large number of persistently symptomatic residents largely from the Railway Colony of Bhopal and who presented at the KEM hospital in Bombay from 7^{th} to 90^{th} day of the toxic gas exposure, formed the study cohort. Subjects were followed up at 3, 6, 12, 18, and 24 months of the initial study, using a clinical respiratory questionnaire modeled on BMRC questionnaire and used earlier on occupational diseases[3]. In addition to physical examination and chest radiography, spirometry (flow/volume loops) before and after inhalation of nebulised bronchodilator aerosol were carried out.

Minute ventilation, oxygen uptake at rest and submaximal exercise (with clinical end point at 4-5 minutes), arterial blood gases at rest and exercise, COHb and MetHb were measured at 0 and 3 months only in selected abnormal subjects. Clinical grading of respiratory illness was done on the basis of the number and severity of symptoms; a score upto 2.0 was taken as mild, 3-4 as moderate and above 4 as severe respiratory illness.

From the flow/volume (F/V) loop, manually V_E and V_1 25, 50, 75 per cent, PEFR, and PIFR were calculated; the transducers were calibrated before and after each reading and an intergrator was used for deriving the volume. Oxygen uptake was measured from the collected expired air in a Douglas bag and analyzing it for oxygen. The chest radiographs were read together by two observers and classified as normal, emphysema, cardiovascular changes, parencymal and interstitial deposits. The latter were categorized as punctate, linear, micro-nodular or reticular along with their zonal distribution.

Serial observations at three months subsequently, included in addition psychiatric, psycho-social and personality dysfunction in a group of cooperative patients. Statistical analyses were done by using student t-tests, proportional Chi Square tests and antibody titres by linear regression.

RESULTS

The main purpose of the present study was to understand the pattern of lung disease caused by the inhalation of MIC/toxic gas in the Bhopal Gas Disaster. Table 8.1 shows distribution of age, gender and clinical severity of initial illness of the original cohort studied at KEM Hospital at Bombay. In comparison with the initial severity of illness when these cases were seen at the KEM Hospital, 69% of them had clinically improved, 4% had worsened, while the remaining remained stable.

Table 8.1 Age, Gender and Clinical Severity Distribution of 113 Toxic Gas Exposed Subjects of Original Cohort

Age/Yrs	Total (100%)	<20	21-40	41-50	>50
Male	87 (77%)	4	38	28	17
Female	26 (23%)	6	19	1	-

Clinical Severity of Initial Illness

Mild	Moderate	Severe	Total
30 (27%)	57 (50%)	26 (23%)	113 (100%)

Table 8.2 lists the sequential patterns in chest, neurological and psychosomatic symptoms. Under 6 assessments done in 2 years on this cohort, 87 at 24 months and 68 at 12 months were re-studied. The psycho-somatic evaluation was not done at the first stage as the subjects were too ill, too near the tragic episode; it was also not possible due to poor comprehension to obtain cooperation in a proportion of cases.

Table 8.2 Sequential Patterns in Clinical Symptoms in the Original Cohort

	Period (months) from the initial study (n – subjects)					
Symptoms (%)	**0 (113)**	**3 (79)**	**6 (56)**	**12 (68)**	**18 (68)**	**24 (87)**
Respiratory						
Cough	98	51	41	72	42	70
Sputum	42	44	36	8	23	48
Dyspnoea	97	86	89	97	86	94
Chest pain	69	51	39	48	51	60
Resp. score	2.92±1.55	2.32^{x}±1.34	2.05^{x}±1.17	2.12^{x}±1.13	2.82±1.20	2.90±1.27
Neurologic	x Significantly better : ($p<0.05$)					
Muscle weakness	32^{x}	83	75	70	91	90^{x}
Poor memory	29^{x}	40	25	28	42	59^{x}
Poor concentration	11	30	12	47	12	8
Tremors	3	25	23	6	10	25
	x, $p<0.05$ (significantly worse)					
Psychiatrist's						
Assessment	-	58	40	40	56	60
Body ache	-	8	35	42	24	15
Insomnia	-	29	42	42	26	58
Headache	-	16	16	30	24	47
Joint pains	-	7	12	10	12	51
Apathy	-	16	15	12	43	1
Tiredness	-	19	15	12	43	-
Giddiness	-	14	25	18	0	24

Thus, overall respiratory symptom score which had improved at 3, 6 and 12 months, later worsened significantly. The commonest symptom was "dyspnoea on exertion" which did not show much improvement, paroxysmal component was unusual. These subjects received antibiotics and bronchodilators intermittently but the symptoms persisted. From neurologic

symptoms spontaneously elicited, muscle weakness and poor memory became worse and more frequent. Several more symptoms were elicited by a psychiatrist. Perhaps some of these were influenced by apprehensions in the legal compensation case.

Table 8.3 presents the psychiatric abnormalities as assessed by psychiatrists and by their social worker. It can be seen that only 19 to 27% of the patients 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 reduced over 2 years ($p<0.05$). Simultaneously, those with mild abnormalities increased.

Table 8.3 Patterns in Psychiatric Abnormalities

	Intervals in Months After The Initial Study				
Psychiatrist assessment	3	6	12	18	24
No. studied	60	37	42	63	60
Normal %	23.3	27	26.2	19	20
Anxiety %	8.3^{x}	5.4	11.9	25.4	15
Depression %	15^{x}	27	21.4	19	36.7^{x}
Mixed %	53.3^{+}	40.5	40.5	36.5	28.3^{+}
x, + $p < 0.05$					
Grading by Hamilton scores					
No. studied	48	36	36	48	60
Anxiety (%)					
Nil (1-12)	45.8^{x}	38.8	27.7	22.9^{x}	26.6^{x}
Mild (-24)	20.8	22.2	19.4	52.1	34.4
Moderate (-36)	33.3	27.7	47.2	22.9	28.1
Severe (36+)	0	11.1	5.5	2.1	10.9
Depression (%)					
Nil (1-15)	65.3^{+}	51.4	37.8	45.8^{+}	46
Mild (-25)	24.5^{x}	21.6	13.5	33.3	34.6^{x}
Moderate (-35)	6.1	21.6	37.8	16.7	12.7
Severe (36+)	4.1	5.4	10.8	4.2	6.3
+, x $p < 0.05$					

Table 8.4 presents results of personality dysfunction and psycho-social studies obtained after filling a detailed proforma and checking. The former shows large post- exposure abnormalities. In 6 categories there was significant improvement best seen at 18 month stage. Table 8.4 shows increased prevalence of abnormal relationship after gas exposure. These assessments were omitted in a few where not applicable (e.g., job, marital). The total abnormality score at 3 and 12 months correlated significantly with FVC and FEV_1, suggesting that these abnormalities were a consequence of pulmonary disability.

Table 8.4 Sequential Patterns in Personality and Psychosocial Function in Toxic Gas Exposed Subjects

	Months Interval From Initial Study				
Personality dysfunction^{+}					
No. studied	3	6	12	18	24
Abnormal %	60	59	72	69	65
Irritability	75	70	72	58	64
Poor concentration	70	56	67	45^{x}	52
Indecision	60	46	51	32^{x}	45
Poor adjustment	52	51	47	26^{x}	25^{x}
Unstable relationship	50	46	53	36	40
Emotional ability	45	26	15	2^{x}	-
Over dependence	40	42	33	35	46
Hypersensitiveness	68	49	47	38^{x}	48

Can't take frustration		75	61	72	55[x]	60
x Significant improvement over 3 months status ($p < 0.05$) + Pre-exposure status assessed as generally better						
[@]Psychosocial function*						
abnormal relationship %	**Pre-exposure**					
Family	(91)					
Interpersonal	4	62	59	62	44	55
Social	4	67	49	46	20	26
Job	0	58	54	50	49	44
Marital	12	70	73	78	61	74
Sexual	6	17	26	29[+]	18	18
	1	67	41	55[+]	54	52

+ Omitted in some subjects (up to 10) as not applicable
@ These assessments missed in some as not cooperative
Pre-exposure and all post-exposure 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^1 (p<0.01; r = 0.56 and 0.73 respectively)

Radiographic and Lung Function Changes

Table 8.5 lists chest radiographic patterns. Only 2 to 4% films over 2 years were read as normal by agreed criteria. The proportions with overinflation reduced along with pleural scars, heart enlargement and consolidation at 6 months or later (p<0.05). At the early stage, only a few consolidations responded to antibiotics and in one case distinct calcified scars developed at the right base. The main changes seen were interstitial shadows. These 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 18/24 months, as also micronodular ones at 12 months or later (p<0.05 of both).

Table 8.5 Serial Radiographic Patterns in Toxic Gas Exposed (113) Cohort

Period/Month	0	3	6	12	18	24
No. studied	113	79	56	68	68	87
Normal %	2	2	4	0	0	3
General Abnormalities %						
Over inflation	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	4	3	3
Interstitial Deposits %						
Zonal Distribution						
1 - 2	36	25	24	9	36	26
3 - 4	40	49	48	64	59	51
5 – 6	24[+]	26	24	27	5[+]	20
+ $p < 0.05$						
Type						
Linear	82	64	86	92	94	94
Punctate	37	43	28	58	20[@]	16[@]
Reticular	27	6	16	14	23	24
Micronodular	27	32	36	14[@]	3[@]	8[@]
Less often [@] $p < 0.05$						
Change from '0'						
Better	-	64	66	62	67	58
Worse	-	6	20	11	10	12

Table 8.6 Sequential Lung Function Trends in Toxic Gas Exposed (113) Cohort

Period/Months	**0**	**3**	**6**	**12**	**18**	**24**	**Significance**
No.	113	79	56	68	68	87	
FVC$^{\#}$ (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	+ p<0.05
a) $FEV_1^{\#}$ (L)	1.98^{x}±0.67	1.97±0.62	1.93±0.57	2.24^{x}±0.60	2.26±0.59	2.14±0.62	x p<0.05
VC obs/pred. %	70.3±16.9	70.1	67.3	93.3	99.9	87.9	
PEFR$^{\#}$ (L/min)	362.3*±128	403±123	412±100	444±105	469*±90	467±106	*P<0.05
# similar results if age-height-gender standardized							
FEV_1/FVC%	*97±4	96±5	97±6	*83±8	79±9	83±10	*P<0.05
Bronchoreversibility 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	N.S.
$MEF_{25-75\%}$ (L/min)	200±82	213±93	207±70	170±79	144±76	150±72	N.S.
$MEFR_{200-1200}$ (L/min)	234±112	256±116	249±96	265±109	272±109	241±118	N.S.
b) Gas exchange MV (L/min)	8.45±3.27	9.45±2.24	10.29±1.84	9.96±2.16	10.45±1.49	8.94±2.54	N.S.
VO_2 (ml) Rest VO_2 (ml) Exercise	198*±58 1123±280	227*±50 1157±403	218±52 -	236±45 -	243±43 -	244±102 -	*p<0.05 -
PaO_2 (mm Hg)	100.9±12.7	88.8±20.3	-	94.1±12.4 (22)	93.8±10.6 (18)	94±9.8 (16)	
$PaCo_2$ (mm Hg)	33.3°±3.7	33.3±4.6	-	33.6±3.1	34.1±1.4	38.2°±4	°p<0.05
PH	7.49^{++}±0.05	7.46±0.06	-	7.43^{++}±0.04	7.42±0.04	7.39^{++}±0.03	++p<0.05
COHb No.	5.97$^{\$}$±11.1 (70)	2.28$^{\$}$±1.43 (71)	-	2.26±1.84 (58)	2.29±1.29	2.28±1.48	$p<0.05
MetHb	1.76^±0.74	0.88^±0.73	-	0.66±0.27	0.40±0.27	0.38±0.17	^p<0.05

MEF200 – 1200 – Maximum expiratiry flow rate at 200-1200 ml of FVC
MEFR 25-75 – Maximum mid-exfiratirory flow rate

Table 8.6 shows the mean trends in lung function and arterial blood gases. While at 0 and 3 months, all subjects cooperated with the latter test, at later periods (not done at 6 months) this was restricted only to more abnormal subjects, Resting oxygen uptake at rest did not show further change after 3 months, while exercise VO_2 increased at 3 months (paired comparison in 44 subjects : 1123±280 ml at 3 months ($p<0.05$). Arterial PO_2 at rest did not change significantly but PCO_2 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 ($p<0.05$). These values were not related to the initial clinical severity. Table 8.6.also lists lung function as true values. If these are standardized for age, height and gender, the conclusions did not change. If one restricts the analysis to a common group, the trends seen were similar (but it seemed that improved cases defaulted more often). Thus, FVC, FEV_1 improved by 12 months then declined later. The PEFR values increased by 12 months and were maintained. $MEF_{25-75\%}$ did not improve as also $MEFR_{200-1200}$. There was a significant reduction of FEV_1/FVC% by 12 months which persisted. Significant bronchodilator response was seen in a small proportion of cases which did not seem to accentuate later. Initially, only 11.6% showed an improvement in FEV_1 (between 11-20%), but in 8.9% this was more than 20%. At 3 months, the increase was 7.7 and 8.8 percent respectively. Thus, there seemed to be no increase in asthmatic tendency after the toxic gas exposure. In 10 cases tested for histamine airway reactivity, 5 reacted at 1 mg/ml concentration ($PC_{20}FEV_1$) while 3 showed PC_{20} at 5 mg/ml.

Pathologic and Immunologic Studies

These were reported elsewhere[4,12]. Lung histology in closed needle (n=3) biopsies showed collagenous tissue. In 3 open biopsies, mild septal and pleural fibrosis, perivascular and peribronchiolar fibrosis, active bronchitis, inflammatory interstitial exudates, distended bronchioles filled with mucinous material with interstitial scarring and thickened muscular vessels were seen. Fibreoptic bronchoscopy findings (in 8 done at 4 weeks), showed distorted airway lumen and mucosal swelling, lymphoid hyperplasia (3), ulceration (2) and patchy congestion (3), broncho-alveolar (BAL) studies done in 14 cases showed high total cell count in all, with neutrophil excess (9), macrophage increase (2), eosinophil excess (1) and lymphocytosis (1).

Table 8.7 Immunologic Results in Toxic Gas Exposed Subjects

Period/Month	0	3	6	12	18	24
No.	63	79	66	99	25*	17*
Total IgE I.U.	1230±1411	894±979	667±832	711±772	618±678	973±671
Restricted to abnormals						
RAST binding IgE	2.31±2.95	2.33±2.65	2.74±3.07	3.68±4.95	-	-
Control IgE	-	-	424±1198 (12)	305±1016 (39)	-	-

Immunological studies in 99 subjects done at intervals are shown in Table 8.7. Total IgE levels showed high values (statistically not significant) initially which later declined. Preliminary studies showed that antibodies specific to MIC (as GSA or HAS) 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. Mean RAST IgE binding revealed levels from 2.31±2.95% ('0') to 3.68±4.95% (12 months). While these were related closely to total IgE values, both these were not related to clinical or functional changes seen. In 11 cases, MIC specific antibodies were detected (IgM : 7, IgE : 4, IgG : 6); in many on several occasions. Thus, in 1 case antibodies were detected one year after exposure but in most these were found in sera taken within 3 months. In 10 cases with clinically adequate data, 4 had severe and 6 moderate initial illness. Radiographically, 1-3 zones showed interstitial deposits in 3 and 4-6 zones in 7 cases. Generally it appeared that those more ill initially but who improved later, showed positive antibodies. These findings with low positive titres may have medicolegal significance for cause and effect relationship.

Defaults and Relationship to Clinical and Functional Sequence

Though it was planned to have a full follow up for 2 years in 6 phases, this could not be achieved. At one and two year stage we followed 68 and 87 subjects respectively. Of these, those who were assessed functionally and clinically for at least on 2 subsequent occasions were included as regular cohort (n=81). When these were compared, it was seen that defaulters (n=32) were slightly less abnormal initially and improved better. On preliminary analyses, it looked that while many showed improvement till 12 months and somewhat deteriorated later; there were patterns : stable, improving, worsening, fluctuating and improvement followed by deterioration. On the overall behaviour, about 25% of them were constantly improving and one half belonged to the last category. Trend of change in 15 parameters was studied and the results are shown in Table 8.8. It is seen that all parameters did not behave identically e.g. cough and dyspnoea showed different trends as also FVC, PEF and $MEF_{25-75\%}$. The trends for COHb and MetHb showed large improvement. A fluctuating behaviour was seen in 20 to 50 percent subjects in various parameters.

RESULTS In Regular Cohort (N=81)

These are presented in Tables 8.9 and 8.10. Table 8.9 shows (SD omitted as similar to Table 8.7) that despite the data being restricted the trends for various parameters are similar; so also the significance of differences. Table 8.10 gives results of depression, anxiety scores and IgE. Again the changes were identical to those in the original cohort.

Table 8.8 Graphic Trends in Toxic Gas Exposed Subjects (113) with Acceptable Patterns

Pattern parameters	No.	Stable	Improving	Worsening	Improvement and then worsening	Fluctuating
Clinical	93	45+(48.4)	22(23.7)	7(7.5)	-	19(20.4)
Dyspnoea	90	16(17.8)	8(8.9)	13(14.4)	8(8.9)	45(50)
Cough	91	21(23.1)	14(15.4)	11(12.1)	10(11)	35(38.5)
Sputum	92	35(38.0)	26(28.3)	6(6.5)	0	17(18.5)
Lung signs	91	5(5.5)	19(20.9)	19(20.9)	13(14.3)	35(38.5)
X-ray : zones						
Lung Function	92	13(14.1)	26(28.3)	0	22(23.9)	31(33.7)
FVC	91	31(34.1)	26(28.6)	1(1.17)	14(15.4)	19(20.9)
FEV_1						
Broncho-reversibility	85	74(87.1)	4(4.7)	7(8.2)	1(1.2)	-
FEV_1	88	13(14.8)	5(5.7)	37(42.1)	18(20.4)	15(17.1)
$MEFR_{0.25-0.75}$	91	17(18.7)	19(20.9)	9(9.4)	17(18.7)	29(31.9)
$MEFR_{200-1200}$	91	12(13.2)	50(55.0)	2(2.2)	5(5.5)	22(24.2)
PEFR	91	27(29.7)	12(13.2)	15(16.5)	-	15(16.5)
MV	91	6(6.6)	4(4.4)	32(35.2)	9(9.9)	40(44.0)
VO_2	77	11(14.3)	42(54.6)	8(10.4)	-	16(20.8)
COHb	85	2(2.4)	60(70.6)	2(2.4)	-	21(24.7)
MetHb						

+ No. followed by percent values in bracket

Table 8.9 Mean Trends in Lung Function in the Regular Cohort (81 Subjects)

Period/Months	0	3	6	12	18	24
No. studied	81	69	55	69	65	81
FVC Lit.	2.02	2.02	1.96	2.68	2.84	2.59
FEV_1 Lit.	1.93	1.95	1.91	2.23	2.26	2.14
FEV_1/FVC %	95.5	96.1	75.2	83.1	79.8	82.3
Broncho-reversibility %	5.7	5.9	5.1	5.5	3.8	5.8
$MEF_{25-75\%}$ Lit/m.	194	210	204	168	144	147
$MEFR_{200-1200}$ Lit/m.	227	253	248	263	272	242
PEFR Lit/min.	363	400	410	445	471	466
MV Lit/min.	8.35	9.52	10.31	10.02	10.46	8.85
PaO_2 mm Hg	101.4	93	-	94.1	93.8	94.1
$PaCO_2$ mm Hg	33.5	31	-	33.5	34.1	38.3
Pha	7.49	7.47	-	7.43	7.39	7.38

SD omitted as mostly similar to Table 8.7

Table 8.10 Sequential Trends for Anxiety, Depression and IgE Level in the Regular Cohort (81 Subjects)

Period/Months	3	6	12	18	24
No.	50	43	50	40	58
Hamilton scores					
Anxiety	15.3	19.5	19.6	19.1	20.1
Depression	12.1	16.5	17.2	14.3	16.3
	0(48)	3(53)	6(52)	12(60)	
IgE Units	1355	950	789	648	

SD similar to values on Table 8.7

DISCUSSION

As findings of the present study upto 6 months have already been published[1-2], it is fair to state that earlier evidence of interstitial, restrictive lung pathology with small airway disease was confirmed. Later, the airway component seemed to have progressed leading to a fluctuating clinical course with persisting disability. There was persistent flow rate abnormalities particularly for $VE_{75\%}$.

Studies done by Alarie et al[5] indicated that severe airway obstruction persisted after a single MIC exposure (37 PPM for 3 hours) and recovery from pulmonary effects was very slow. It was considered to be slower than with H_2SO_4, TDI or wood smoke. In view of the controversy about cyanide like effects (e.g. persistent muscle weakness) in Bhopal subjects, evidence of early rise in COHb and MetHb may be important. Earlier, isocyanates have been associated with occupational asthma.

Bucher et al[8] observed granulomatous inflammation with persistent lung damage, intraluminal airway fibrosis and bronchiolitis after 2 hour exposure to MIC in rats. Their studies on repeated exposure to 1-6 PPM MIC did not result in significant direct effects on non-respiratory tissues. The observations of the present study confirm this pattern and both data show evidence of chronic pulmonary damage.

SUMMARY AND CONCLUSIONS

Anderson et al[11] have presented some data from Bhopal community studies which indicated the differences in morbidity according to wind direction. Thus, Railway Colony situated to south east suffered a high mortality. The follow up data indicates that behaviour of affected subjects though varying in the initial severity of illness, have a similar course, in later periods.

1. The study cohort of 113 toxic gas exposed subjects came largely from the severely affected Railway Colony of Bhopal. They were studied within 90 days of the exposure. 79, 56, 68, 68 and 87 of them were followed up with clinical, lung function, radiologic and immunologic studies at 3, 6, 12, 18 and 24 months respectively.
2. While initially all had eye problems, the dominant symptoms which persisted were exertional dyspnoea (86-97%), cough (41-90%), chest pain (48-69%), sputum (25-48%) and muscle weakness (32-91%). A large number showed clinical evidence of persistent depression mixed with anxiety, causing serious disburbance of psychosocial and personality parameters.
3. The early chest radiographic changes were oedema, consolidation, overinflation, enlarged heart, and pleural scars. The persistent abnormalities were interstitial deposits which improved over time in 58 to 67% cases.
4. Spirometry (flow/volume curve) showed mainly restrictive pattern, small airway narrowing with little bronchoreversibility. Exercise test showed difficulties of oxygen exchange. The latter improved at 3 months; and spirometry improved over 12 months only to decline later again. The expiratory flow indices pertaining to large and medium airway function improved but not those of small airways.

5. On follow-up, only 18 to 48% cases remained clinically stable while 18 to 50% clinically were fluctuating. For lung functions, 17 to 32% were fluctuating.

ACKNOWLEDGEMENTS

We thank Dr.G.B.Parulkar, Dean for permitting this study. We sincerely appreciate continued support of Indian Council of Medical Research, New Delhi. We also wish to acknowledge technical support of Dr.R.K.Agarwal, Chief Medical Officer, Central Railways. Several subjects who made this follow up at a distance of 500 miles possible, and administrative and secretarial help of Mrs.Gracy Zaccheus and Mrs.Sudarshana Joshi.

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Chapter 9

Pregnancy Outcome in Women Exposed to MIC/Toxic Gas

OBJECTIVES

To monitor the adverse effects in pregnant women who were exposed to methyl isocyanate (MIC)/toxic gas at Bhopal, in comparison to the pregnant women in an unexposed/control area.

MATERIAL AND METHODS

The study was carried out in 10 severely affected areas of Bhopal city, located around the Union Carbide Factory identified on the basis of ICMR categorisation. The areas included : J.P.Nagar, Kazi Camp, Tila Jamalpura, Shahjahanabad, Straw Product, Bus Stand – Ibrahimganj, Kenchi Chhola, Railway Colony, Station Bazaria and Chandbarh. Door-to-door population survey was carried out during April - May, 1985 to identify women who were pregnant at the time of gas leak, on the basis of last menstrual period being before 18th November, 1984.

As this made the study partly retrospective and partly prospective, the identified study population were divided into the following three groups :

1. Those who aborted between December 3, 1984 and the date of the commencement of survey (381).
2. Those who delivered within this period (934).
3. Those who were found to be pregnant at the time of survey (1251).

Details on abortions and on women who had delivered before the commencement of the survey were obtained on the basis of history given by the woman and confirmed by interview of neighbours and a review of the records of the nursing home and hospitals wherever possible (125 cases). Spontaneous abortions were reconfirmed through a quick survey (as suggested by the concerned Project Advisory Committee in December, 1985). The women who were pregnant at the time of survey were prospectively followed till delivery. All the babies born since December 3, 1984 and who were alive were examined to detect congenital malformations, both major and minor, if any. In cases, where the child had died or there was a still birth, a set of photographs of common congenital malformations were shown to either parents or others who had seen the body of such a child, to verify the presence or absence of congenital malformations.

A control unexposed areas of similar socio-economic strata was selected in the following localities of Bhopal : Anna Nagar, Vishwakarma Nagar, Habibganj, Janta Colony (near Arera Colony), Panchsheel Nagar, Harshvardhan Nagar, Ambedkar Nagar, Banganga and Roshanpura. Study of women in the control area could not be done simultaneously as it was more important and urgent to survey the pregnant women in the affected area. Thus, study in the control area was started only a year later, taking 3rd December, 1985 as the cut-off date

and all women pregnant on this date were registered to obtain a similar cohort in respect of period of gestation.

The study in the control area was thus totally prospective. A door-to-door survey was carried out to identify the pregnant women, and carefully follow them up for outcome of pregnancy. Statistical analysis of data was done using the Student's 't' test and proportion test, for testing the difference between average and observed rates respectively.

RESULTS AND DISCUSSION

The total number of households surveyed were 18,978 with a population of approximately 86,000 in the affected area and 13,539 households covering a population of approximately 60,000 in the control area. Of these, 2566 women from the affected areas and 1218 women from the control areas were identified as pregnant as on December 3, 1984 and 1985 respectively, and the outcome of pregnancy was studied. There were 2153 deliveries in the affected area, of which 1071 (49.7%) were conducted in hospitals and 39 (1.8%) were conducted in MCH Centres and Nursing Homes, the remaining 1043 (48.4%) were conducted at home. There were 1180 deliveries in control area, 627 (53.1%) were conducted in Hospitals, one (0.08%) in a nursing home and the remaining 552 (46.8%) at home.

Socio-economic profile. Most of the women were from the lower socio-economic strata. The mean per capital monthly income was assessed at Rs.122±69 in the control area and Rs.96±87 in the affected area. Though the *per capita* income was slightly higher, the literacy rate was found to be marginally lower in the control area (32.5%) than in the affected area (39.4%).

Religion. The proportion of Muslims was considerably higher in the affected area (40.3%), as compared to the control area (14.4%). It is noteworthy that no other area of similar socio-economic strata with comparable proportion of Muslims could be found within the control/unexposed areas of Bhopal.

Consanguinity. This was observed to be 15.6% in the affected area as compared to 6.7% in the control area, probably due to higher proportion of Muslims in the affected area.

Age. The mean age of women in the affected and control areas was 24.9 and 24.4 years respectively. In the affected area, 341 (21.6%) women were aged 30 years or above, as compared to 74 (15.7%) in the control area, the difference being statistically significant ($p<0.001$).

Previous obstetric history. Previous obstetric history was taken for all the women included in the study. Average parity of the overall sample in the affected area was 2.8 of which 2.5 were live births, 0.04 still births, 0.23 were spontaneous abortions, and 0.02 were induced abortions. In the control area the average parity was 2.1, of which 1.9 were live births, 0.03 were still births, 0.17 were abortions. The average number of living male and female children was 1.2 each in the affected area, and 0.7 and 0.9 respectively in the control area.

Gestation period (as on December 3). The period of gestation at which women entered the cohort was considered important, as the outcome of pregnancy is associated with this factor. There was considerable variation in the distribution of women according to gestation on 3rd December in the affected and control areas. There were 57.3% pregnancies with period of gestation up to 20 week on 3rd December, 1984 in the affected area. The corresponding figure for control area was 39.9%. Percentage of women with gestation 21-27 week were

15.7 and 22.22 in the affected and control areas respectively. The remaining 27.0% pregnancies in affected area and 37.9% pregnancies in control area were of gestation 28 week or above. This difference may be due to the fact that those women (from the affected area) who were in the third trimester of pregnancy perhaps went elsewhere for their delivery recognizing that pregnancy constituted increased risk particularly in the wake of the general atmosphere of shock, fear and controversies prevalent at the time of the gas disaster. Those women obviously could not be included in the study as they were not present at the time of survey (Table 9.1).

Table 9.1 Period of Gestation of Study Groups as on 3rd December, 1984/1985

Period of Gestation (weeks)	Affected Area (Number)	Control Area (Number)
<12	934 (36.4)	250 (20.6)
13 – 20	534 (20.9)	235 (19.3)
21 – 27	401 (15.7)	270 (22.2)
28 – 36	450 (17.6)	307 (25.2)
>37	242 (9.4)	154 (12.7)
Total	2561 (100)	1216 (100)

Gestation period not known – 5
Figures in parentheses are percentages

Outcome of Pregnancy

Abortion. Abortion is defined as termination of pregnancy before 20 week of gestation. Only those women who were up to 20 week of gestation on 3rd December, 1984/1985 were considered to be at risk of abortion. These included 1468 women in the affected area against 485 women in the control area. Among these, 355 (24.2%) pregnancies from the affected area and 27 (5.6%) pregnancies from the control area ended in spontaneous abortions (Table 9.2). A diagnosis of abortion was recorded only when the woman gave history of amenorrhea of at least 8 week and/or had actually observed expulsion of products of conception. All spontaneous abortions were confirmed through a re-surgery done by doctors, using a detailed information check list. In 125 cases of spontaneous abortions, records were available from hospitals or doctors. The history of D&C was confirmed from hospital records (43 cases). The abortion rate was significantly higher in the affected area ($p<0.001$ Table 9.2) than the control area.

Table 9.2 Outcome of Pregnancy

	Affected Area	Control Area
Total number of pregnancies	2566	1218
Number of women at risk of abortion	1468	485
Number of spontaneous abortions	355	27
Abortion rate (%)	24.2*	5.6*
Number of induced abortions	26	3
Intermediate foetal death (21-27 week of gestation)	32	8
Number of deliveries	2153	1180

*$p<0.001$

In the affected area, abortion rate was 32.5% in women (341) of age 30 years or above compared with 22.1% in women below 30 years. This difference was statistically significant. It is noteworthy that no case of spontaneous abortion was reported from women (74) 30 years or above, in the control area.

Religion and consanguinity were not found to have any association with the abortion rate, for instance in the affected area the abortion rate was 26.3% among Hindus and 21.9% among Muslims.

In the control area, the abortion rate which was slightly higher among the Muslims (9.1%), was not significant as compared to 5.0% amongst Hindus (Table 9.3). Among consanguineous and non-consanguineous marriages abortion rates were 26.6 and 23.9% respectively in the affected area, and 6.6 and 5.6% respectively in the control area (Table 9.4). Abortion rates were significantly higher in the affected area irrespective of religion or consanguinity.

Table 9.3 Spontaneous Abortions in Relation to Religion

Religion	Affected Area			Control Area		
	At risk of abortion	Number of spon. abort.	Rate %	At risk of abortion	Number of spont. abort.	Rate %
Hindu	832	219	26.3	402	20	5.0
Muslim	607	133	21.9	77	7	9.1
Others	29	3	10.3	6	-	-
Total	1468	355	24.2	485	27	5.6

Table 9.4 Spontaneous Abortions in Relation to Consanguinity

Consanguinity	Affected Area			Control Area		
	At risk of abortion	Number of spon. abort.	Rate %	At risk of abortion	Number of spont. abort.	Rate %
Yes	248	66	26.6	33	2	6.6
No	1208	289	23.9	448	25	5.6
Not known	12	-	-	4	-	-
Total	1468	355	24.2	485	27	5.6

Intermediate foetal deaths. In the affected area, 32 (1.2%) intermediate foetal deaths (pregnancy termination between 21-27 week) were recorded, as compared to 8 (0.7%) cases in the control area (Table 9.2).

Still births. Taking into consideration the pregnancies which terminated at 28 week of gestation and above, there were 2153 deliveries in the affected area, of which 56 were still births and 2117 live births as 20 deliveries had resulted in twin births. This gave a still birth rate of 2.57%. In the control area, the total number of deliveries at or after 28 weeks of gestation were 1180. Of these, 27 were still births and 1160 live births giving a still birth rate of 2.27%. No difference was observed in the still birth rates in the affected and control areas. In the control area, 7 deliveries (0.59%) resulted in twin births as compared to 20 (0.9%) in the affected area, the difference being statistically not significant (Table 9.5).

Congenital malformations. There were 31 congenital malformations in the affected area in 2173 births. In the control area 15 of a total of 1187 births showed congenital malformations, giving a congenital malformation rate of 14.2 per 1000 births and 12.6 per 1000 births in the affected and control areas respectively – statistically not significant (Table 9.5). Details of the nature of congenital malformations observed in the two areas are depicted in Table 9.6. As in case of abortions, religion did not show any significant correlation with congenital malformations. The latter were found to be slightly higher in consanguineous as

compared to non-consanguineous marriages in both the affected and the control areas. It was 1.9 and 2.5 per 1000 births for consanguineous marriages and 1.4 and 1.2 per 1000 births in non-consanguineous marriages in the affected and control areas respectively. These differences were statistically significant.

Table 9.5 Neonatal Outcome

	Affected Area	**Control Area**
Total number of deliveries	2153	1180
Number of twin births	20	7
Number of live births	2117	1160
Number of still births	56	27
Still birth rate/1000 deliveries	26.0	22.9
Number of early neonatal deaths (0-7 days)	95	33
Total perinatal loss	151	60
PMR/1000 births	69.48*	50.54*
Number of neonatal deaths (0-28 days)	129	52
NMR/1000 live births	60.99**	44.8**
Number of congenital malformations	31	15
Rate/1000 births	14.2	12.6

P values *<0.001; **<.001

Table 9.6 Congenital Malformations

Type of malformations	**Exposed Area**	**Control Area**
Congenital talepes equinovarus	13	02
Congenital heart disease	07	03
Meningo myelocele	02	--
Exomphalus	01	--
Micro ophthalmia with lenticular opacity	01	--
Imperforate anus	01*	02
Congenital aplasia of both eyes	01	--
Haemangioma scalp	01	--
Hirschsprung disease	01	--
Hypospadiasis	01+	01
Cleft lip with cleft palate	01	--
Rocker bottom foot	01	--
Multiple congenital anomalies	--	02
Anencephaly	--	02
Microcephaly	--	01
Polydactyly	--	01
Foetal ascitis	--	01
Total	31	15

*With recto-vaginal fistula

+With absence of external ear

Perinatal and neonatal mortality. Of the 2153 deliveries in the affected area, 2117 were live births (including 20 twin deliveries). Of these, 95 babies died within 7 days of birth and 34 died between 8 to 28 days of birth, giving a perinatal mortality rate of 69.48 per 1000 births and a neonatal mortality rate of 60.9 per 1000 live births. In the control area, of the 1160 live births (including 7 twin deliveries) out of 1180 deliveries, 33 babies died within 7 days of birth while another 19 died between 8-28 days, giving a perinatal mortality rate of 50.54 per 1000 births and neonatal mortality of 44.8 per 1000 live births. Both perinatal and neonatal mortality rates were significantly lower in the control area than in the affected area (Table 9.5).

Babies who survived beyond 28 days (1980 babies from the affected area and 1108 babies from the control area) were followed up for morbidity and mortality during infancy.

DISCUSSION AND CONCLUSIONS

The abortion rate was more than four times in the toxic gas affected area as compared to the control area. Abortion rate in the affected area was significantly higher in women 30 yeas of age or above (32.5%) as compared to women below 30 years of age (22.1%). There was no case of abortion in women 30 years or above in the control area. Abortion rate in the affected area after standardizing for age according to the control area was found to be 23.6% as compared to 5.6% in control area, which was still very high.

Still birth rate was found to be similar in the affected and control areas, but both perinatal and neonatal mortality rates were higher in the exposed area. In relation to age, perinatal mortality was higher in women of 30 years or above and there were 20.4% women in that age group in affected area as compared to 16.4% in the control area. Standardised perinatal mortality in exposed area considering control area as standard was seen to be still higher. In the control area, the perinatal mortality was not higher in the older age group. After standardization the neonatal mortality in the exposed area came down to 60.6 from 60.9 per 1000 live births but was still significantly higher than 44.8 in the control area.

When compared to the national averages, the perinatal mortality was higher in the affected area than the national average of 53.6 per 1000 deliveries but neonatal mortality although higher than the control area was lower than the national average of 67.2 per 1000 live births.

The congenital malformation rate of 14.9 per 1000 birth in the affected area was not significantly different from 12.6 per 1000 births in the control area.

Chapter 10

Health Effects of MIC/Toxic Gas in Children :

1. **FOLLOW UP STUDIES IN CHILDREN 0-5 YEARS OF AGE AT THE TIME OF EXPOSURE**
2. **STUDY OF PULMONARY EFFECTS OF TOXIC GAS IN CHILDREN 6-15 YEARS OF AGE AT THE TIME OF EXPOSURE**

CHILDREN 0-5 YEARS OLD

OBJECTIVES

To study the health effects of toxic gas inhalation.

Study Period : October 1986 to 1990

MATERIALS AND METHODS

All children from one of the severely affected localities (JP Nagar) and an equal number of children from unexposed/control area (Panchsheel Nagar) for comparison were included in the study. Morbidity survey of all children below 3 years of age at the time of exposure was done once a month. Initially, all children were registered by house to house visit and subsequently, morbidity and mortality patterns were inquired from parents or guardians by recall of the past 15 days, by the field investigator and cross checked by Medical Officer on a random sample to minimize chances of error. Surveys were carried out simultaneously in both the affected and control areas to avoid effects of seasonal changes. All children surveyed were clinically examined by a pediatrician once every 3 months, recording the immediate past symptoms for a possible clinical diagnosis.

Anthropometric measurements such as weight and height were recorded every 3 months. Weight was recorded using Tansi scales for those weighing less than 20 kg and weighing machine made by Avery Co. for children weighing more than 20 kg. Length was recorded by an infantometer or by a height scale for children older than 4 years. Two peripheral health centers were established, one each in the affected and control area respectively to facilitate compliance. Hematological investigations such as hemoglobin estimation, total and differential leucocyte counts and skiagram chest were done wherever indicated. Children born after the toxic gas leak were not included in the study.

Analysis of data was done using tests of proportion.

RESULTS

Baseline information regarding families is provided in Table 10.1. It can be seen that 1533 families in the affected area and 2128 families in the control area were surveyed. Most of the children belonged to families of lower socio-economic strata. Distribution of characteristics of children studied are given in Table 10.2. There were 1412 children below 5 years in the affected area and 1268 in the control area. Fifty-one percent in affected and 53% in control

area were males. 98.3% of children from affected area and 1.9% from control area had history of exposure to toxic gas.

Table 10.1 Baseline Characteristics of Study Group

	Affected Area	**Control Area**
Total no. of families	1533	2128
Total no. of family members	7648	9753
Per capita income (Rs/month)		
Less than 50	134 (8.76)	12 (0.56)
51 – 100	1228 (80.36)	1770 (83.1)
151 – 300	138 (9.03)	296 (13.9)
More than 300	28 (1.83)	50 (2.34)

Figures in parentheses are percentages

Table 10.2 Analysis of Registration Data of Children 0-5 Years

		Affected Area	**Control Area**
1.	Total number of children studied	1412	1268
2.	Age group distribution		
	1 Year	318 (22.5)	240 (18.9)
	2 Years	306 (21.6)	330 (26.0)
	3 Years	258 (118.2)	301 (23.7)
	4 Years	260 (18.4)	263 (20.7)
	5 Years	270 (19.1)	134 (10.5)
3.	Sex		
	Male	725 (51.3)	673 (53.0)
	Female	687 (48.6)	595 (46.9)
4.	Type of dwelling		
	Thatched	118 (8.3)	8 (0.6)
	Kaccha	965 (68.3)	753 (59.3)
	Pakka	289 (20.4)	500 (39.4)
	Apartment	40 (2.8)	7 (0.5)
5.	Education of father		
	Nil	638 (45.1)	291 (22.9)
	Upto primary	467 (33.0)	500 (39.4)
	Upto higher secondary	270 (19.1)	400 (31.5)
	College/University	37 (2.6)	77 (6.0)
6.	Education of mother		
	Nil	1016 (71.9)	817 (64.4)
	Upto primary	252 (17.8)	237 (18.6)
	Upto higher secondary	142 (10.0)	189 (14.9)
	College/University	2 (0.1)	25 (1.9)
7.	Occupation of father		
	Unskilled	1182 (83.7)	451 (35.5)
	Semi-skilled	196 (13.8)	662 (52.2)
	Skilled	34 (2.4)	155 (12.2)
8.	History of exposure to toxic gas		
	Affected	1389 (98.3)	24 (1.9)
	Not affected	23 (1.6)	1244 (98.1)

Figures in parentheses are percentages

Symptomatology

Symptoms recorded in detail at monthly morbidity surveys during 1987, 1988 and 1989 are shown in Table 10.3. Respiratory symptoms were the predominant symptoms which varied from 45% to 52% for cold/running nose and 34% to 39% for cough during three years. These symptoms were significantly higher in exposed children compared to control children ($p<0.05$). Prevalence rates of gastrointestinal symptoms (loose motions, pain abdomen and

vomiting), conjunctivitis, ear discharge and superficial skin infections were also significantly higher ($p<0.05$) in exposed subjects than controls. A substantial number of children (14-25%) had fever.

Table 10.3 Symptomatology During Monthly Morbidity Surveys

		April'87–March'88		April'88-March'89		April'89-December'89	
		Affected	**Control**	**Affected**	**Control**	**Affected**	Control
Children surveyed		6670	7469	7190	6515	5274	4719
Symptom analysis							
1.	Fever	24.75%	11.4%	13.9%	8.6%	20.6%	6.05%
2.	Cold/running of nose	48.3%	13.3%	44.9%	15.6%	52.01%	6.77%
3.	Cough	34.8%	12.0%	34.2%	12.8%	38.8%	7.07%
4.	Breathlessness	2.1%	0.3%	1.5%	0.16%	2.32%	0.26%
5.	Vomiting	1.9%	0.9%	1.15%	0.66%	2.17%	0.63%
6.	Loose motions	11.0%	3.15%	6,2%	1.98%	7.50%	1.00%
7.	Pain in abdomen	8.8%	2.2%	7.5%	1.8%	10.67%	1.79%
8.	Stomatitis	0.2%	0.08%	0.2%	0.03%	0.32%	-
9.	Conjunctivitis	9.4%	2.9%	5.2%	0.78%	6.12%	0.51%
10.	Ear discharge	3.6%	0.7%	3.4%	0.98%	4.2%	0.89%
11.	Multiple boils	7.1%	1.8%	6.6%	1.8%	9.05%	1.53%
12.	Skin rashes	2.1%	1.1%	0.8%	0.7%	0.34%	0.04%

Clinical Signs

Prevalence rates of clinical signs such as pallor, finger clubbing, splenomegaly were significantly higher in affected children compared to control children (Table 10.4). Rhonchi and crepitations in chest were also detected in a significantly higher number of affected than control children.

Table 10.4 Clinical Signs During 3 Monthly Examination

		April'87–March'88		April'88-March'89		April'89-December'89	
		Affected	**Control**	**Affected**	**Control**	**Affected**	**Control**
1.	Marked pallor	2.18*	0.16	1.58*	0.05	0.57	-
2.	Matted glands	0.88*	0.16	0.70*	0.20	0.25	-
3.	Clubbing	0.50*	0.16	0.93*	0.15	0.89	0.19
4.	Chest deformity	0.97	0.53	1.3*	0.6	1.75	0.44
5.	Hepatomegaly	0.69*	0.21	0.28	0.10	0.12	-
6.	Splenomegaly	7.76*	1.07	6.63*	0.41	5.66*	0.32
7.	Rhonchi chest	6.08*	0.59	4.57*	0.15	3.86*	0.19
8.	Crepitations chest	10.73*	0.37	7.10*	0.15	5.79*	0.12

*Significantly different from controls

Clinical Diagnosis

Upper respiratory infections (URI) and acute respiratory infections (ARI) like bronchopneumonia and asthmatic bronchitis were found to be significantly more common in children from affected areas (Table 10.5). The prevalence of URI varied from 17 to 28% during 3 year period of follow up compared to 12 to 17% in control areas. ARI was diagnosed in 8-11% of affected children. Eye infections were also more common in affected areas during follow up. There were no consistent pattern with regard to other symptoms during the 3 years of study.

Table 10.5 Clinical Diagnosis

		April'87–March'88		April'88-March'89		April'89-December'89	
		Affected (n=1179) %	Control (n=1071) %	Affected (n=2140) %	Control (n=1928) %	Affected (n=1554) %	Control (n=1560) %
1.	Respiratory illness						
	URI	17*	12	26*	12	29*	16
	ARI	11*	8	9*	2	8*	0.9
2.	Gastrointestinal illness	4	5	3	4.5	3.6	5**
3.	Skin infection	6*	3	6*	3	5.5	4
4.	Eye infection	7	9	4*	2	4*	1.5
5.	Ear infection	4	4	4	3	5*	1
6.	Viral disease	0.43**	-	0.8	7**	0.3	2**
7.	Tuberculosis	1	1	1.6	0.3	1.5*	0.4
8.	Malaria	3	3	6	3	4.5	4
9.	Worm infestation	13*	8	8	9	7*	0.3
	Other diseases						
	Anemia	1	0.4	1*	0.06	0.5	-
	Vitamin A deficiency	7	6	12	16	2	14**
	Other A vitamin	1*	0.3	0.8	0.5	-	-

*Significantly different from controls

Anthropometry

The weight and length of exposed male and female children upto the age of one year at the time of exposure do not reveal any significant difference compared to control area children (Tables 10.6 and 10.7).

Table 10.6 Weight of Children (0-1 year) at the Time of Gas Exposure

Sex	Age group	Affected area		Control area		P value
		n	Mean ± SD	n	Mean ± SD	
Male	43-48 Mths	105	12.26±1.20	62	12.36±1.94	>0.05
	49-54 Mths	161	12.97±1.23	80	12.76±1.77	>0.05
	55-60 Mths	77	13.52±1.26	33	13.77±1.91	>0.05
Female	43-48 Mths	78	12.12±1.38	69	11.90±1.54	>0.05
	49-54 Mths	124	12.69±1.40	106	12.65±1.60	>0.05
	55-60 Mths	68	13.31±1.52	48	13.18±1.51	>0.05

Table 10.7 Height of Children (0-1 year) at the Time of Gas Exposure

Sex	Age Group	Affected Area		Control Area		P Value
		n	Mean ± SD	n	Mean ± SD	
Male	43-48 Mths	105	92.29±3.25	62	91.68±6.59	>0.05
	49-54 Mths	161	95.02±3.18	80	94.50±5.25	>0.05
	55-60 Mths	77	97.33±3.83	33	98.90±5.61	>0.05
Female	43-48 Mths	78	90.97±4.29	69	90.01±5.97	>0.05
	49-54 Mths	124	93.63±4.27	106	93.80±5.68	>0.05
	55-60 Mths	68	95.94±4.69	48	96.28±5.39	>0.05

Current Status (Table 10.8)

By the end of 14 morbidity rounds in March 1988, 42% of affected area children were healthy and 44% were still suffering as compared to control area children of whom 69% were healthy and 22% were suffering. The total number of deaths recorded was 10 in the affected and 12 in the control areas.

Table 10.8 Current Status

		April'87–March'88		April'88-March'89		April'89-December'89	
		Affected	Control	Affected	Control	Affected	Control
1.	Current status						
	Healthy	42%	69%	45%	73%	36%	83%
	Recovered	4%	5%	2%	5%	2%	1%
	Improved	10%	4%	8%	3%	7%	1%
	Still suffering	44%	22%	45%	19%	56%	14%
2.	Number of deaths	10	12	1	2	-	-

By the end of 27 morbidity rounds in March 1989, 45% of children in the affected area were healthy and 45% were still suffering, as compared to 73% of healthy children and 19% still suffering from various illnesses in the control area. One death due to tubercular bronchopneumonia was recorded in the control area.

By the end of 9 morbidity rounds from April 1989 to December 1989, it was found 36% of affected children were healthy and 56% were still suffering as compared to 83% of healthy and 14% children still suffering from various diseases in control area.

CONCLUSIONS

Monthly morbidity surveys by field workers had revealed that respiratory, gastrointestinal and superficial infections (ear, eye and skin) were significantly more in the affected population. However, 3 monthly clinical examination done by pediatricians had shown that predominant illness among the gas exposed children was respiratory illness such as upper respiratory tract infection and acute respiratory infection (bronchopneumonia and asthmatic bronchitis), anthropometric parameters such as weight and length were similar in exposed and control areas. This study also revealed that 44 to 56% of children were still suffering from the consequences of gas exposure.

II. STYDY OF PULMONARY EFFECTS OF TOXIC GAS IN CHILDREN 6-15 YEARS OF AGE AT THE TIME OF EXPOSURE

OBJECTIVES

To study pulmonary effects of toxic gas in children 6-15 years old.

Study Period : April 1986 to August 1987

MATERIAL AND METHODS

All children between 6-15 years of age at the time of toxic gas exposure and residing at JP Nagar - one of the most severely affected areas - were selected for study. An equal number of children of same age group, but not exposed to the toxic gas from Panchsheel Nagar acted as controls. Children whose correct date of birth/age were not known were excluded from study in both groups. Before the study began, one week training with regard to filling of proforma and use of portable spirometer was provided to all medical officers and field assistants by the senior faculty of the Pediatric Department of Gandhi Medical College. In addition, periodic guidance sessions and surprise field checks were also carried out.

All children were registered by a house to house survey. History of exposure to gas, past illness and current symptoms was recorded in a pre-structured proforma. Physical examination including anthropometric measurements were done by medical officers. Pulmonary function tests of forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow rates (PEFR) were recorded in each of the 796 affected and 401 children from control area.

Two peripheral health centers in the affected area and one in the control area were set up for the study. Each center was equipped with one Avery weighing machine and height scales for measuring weight and height respectively.

Table 10.9 Age and Sex Distribution

	Affected Area (n=1601)	Control Area (n=1436)
Sex		
Male	804 (50)	741 (52)
Female	797 (50)	695 (48)
Age distribution		
6 years	258 (16)	7 (0.5)
7 years	200 (13)	70 (5)
8 years	191 (12)	242 (17)
9 years	119 (7)	167 (12)
10 years	177 (11)	231 (16)
11 years	153 (10)	157 (11)
12 years	178 (11)	181 (13)
13 years	118 (7)	125 (9)
14 years	93 (6)	118 (8)
15 years	112 (7)	109 (8)
16 years	2	24 (2)
17 years	0	4 (0.3)

Figures in parentheses indicate percentages

RESULTS AND DISCUSSION

1601 children from affected and 1436 children from control areas were studied (Table 10.9). 804 (50%) from affected and 741 (52%) from control area were males. All children from affected area were exposed to the gas whereas only 1.4% from control area had history of exposure (Table 10.10). 159 children from affected area were residing within one km of the Union Carbide Factory. The mean height in the affected and control children was comparable (Table 10.11).

Table 10.10 Past, Family and Toxic Gas Exposure Histories

		Affected (n=1601)	Control (n=1436)
i.	Past history suggestive of bronchial asthma	15 (0.9)	10 (0.7)
ii.	Past history suggestive of tuberculosis	6 (0.3)	5 (0.3)
iii.	History of atopy in the family	27 (1.5)	30 (2)
iv.	History of exposure to toxic gas	1601 (100)	15 (1)

Figures In Parentheses Indicate Percentages

Symptomatology at the Time of Gas Exposure

Immediate. Immediate respiratory and ophthalmic symptoms following exposure were present in 98-99% of children (Table 10.11). Unconsciousness was reported in 30% of children and 41% were hospitalized within one week. Respiratory symptoms persisted in 70% after one week.

Table 10.11 Symptomatology at the Time of Gas Exposure

Burning in eyes	1589 (99)
Watering from eyes	1596 (99.7)
Redness of eyes	1595 (99.6)
Photophobia	1575 (98)
Cough	1572 (98)
Choking sensation	1576 (98)
Breathing difficulty	1574 (98)
Loss of consciousness	0487 (30)
Hospitalisation within a week	0650 (41)
Death in the family	0288 (18)
Respiratory symptoms after one week	
a. Continued	1116 (70)
b. Disappeared	0482 (30)
c. Not applicable	0003 (1)

Figures in parentheses indicate percentages

1-1.5 years after exposure. Continuous cough at the time of study was persisting in 33% of children and intermittent cough in 37% (Table 10.12). Exertional dyspnoea was reported in 73% children. Other main symptoms were expectoration (26%), wheezing (4%), chest pain (28%), and loss of appetite (40%). Physical findings revealed marked pallor in 0.8% (Table 10.13). Respiratory signs such as rhonchi and rales are found in 1.3 and 2.1% respectively.

Table 10.12 Symptomatology 1-1.5 Years After Exposure

Symptoms	Affected Area (n=1601)	Control Area (n=1436)
Cough		
a. Continuous	532 (33.2)	006 (00.4)
b. Intermittent	618 (38.6)	366 (25.4)
Expectoration	411 (25.6)	041 (02.8)
Wheezing	061 (03.8)	020 (01.4)
Shortness of breath		
a. On exertion	1162 (72.5)	062 (04.3)
b. At rest	024 (1.5)	-
Haemophysis	048 (03.0)	004 (00.3)
Chest pain	445 (27.7)	021 (01.4)
Loss of appetite	643 (40.1)	015 (01.0)

*Sputum for AFB was negative in all cases except in one case.
Figures in parentheses indicate percentages

Table 10.13 Clinical Examination 1-1.5 Years After Exposure

Clinical Findings	Affected Area (n=1601)	Control Area (n=1436)
Marked pallor	13 (0.8)	04 (0.3)
Matted cervical glands	12 (0.7)	09 (0.6)
Clubbing	01 (0.1)	00 (0.0)
Cyanosis	01 (0.1)	00 (0.0)
Chest deformity	49 (3.0)	20 (1.4)
Respiratory signs		
a. Rhonchi	22 (1.3)	07 (0.5)
b. Crepitations	34 (2.1)	04 (0.3)
Organic murmur	04 (0.3)	04 (0.3)
c. Splenomegaly	02 (0.1)	06 (0.4)
Hepatomegaly	21 (1.3)	08 (0.5)

Figures in parentheses indicate percentages

Pulmonary Function Test Results

Table 10.14 shows that mean height of children in the affected and control areas do not show any significant difference. Height is an important determinant of pulmonary function test values. Pulmonary function results are shown in Tables 10.15-19. The mean peak expiratory flow rates in affected and control children were similar ($p>0.5$) (Table 10.15). The mean FVC in affected boys and girls were significantly lower ($p<0.05$) compared to control subjects (Tables 10.16-17). Similarly, mean FEV1 was also significantly lower ($p<0.05$) in affected boys and girls (Tables 10.18-19) than the control subjects.

Table 10.14 Height of Study Subjects for Pulmonary Function Testing

Height range (cm)	Control		Affected		P value
	N	Mean ± SD	N	Mean ± SD	
96-105	7	103.57±2.14	63	102.15±2.64	>0.05
106-115	27	111.51±2.62	168	110.72±2.95	>0.05
116-125	90	120.62±2.60	152	120.77±3.08	>0.05
126-135	99	130.69±2.72	153	130.26±3.22	>0.05
136-145	76	140.68±2.89	142	140.71±3.50	>0.03
146-155	72	149.58±2.93	85	149.47±2.72	>0.05
156-165	30	159.26±2.62	33	159.03±2.75	>0.05

Table 10.15 PEFR (1/min.) in Study Subjects

Height (cm)	Control		Affected		P value
	n	Mean ± SD	n	Mean ± SD	
96-105	07	141.08±29.56	63	132.74±29.11	>0.05
106-115	27	154.47±28.17	168	155.47±26.38	>0.05
116-125	90	187.68±35.55	152	187.17±36.09	>0.05
126-135	99	226.76±41.75	153	220.43±32.70	>0.05
136-145	76	270.16±47.62	142	264.74±54.49	>0.05
146-155	72	309.00±49.45	85	314.69±58.87	>0.05
156-164	30	340.24±51.77	33	372.81±71.96	>0.05

Table 10.16 FVC (ml) in Boys

Height (cm)	Control		Affected		P value
	n	Mean ± SD	n	Mean ± SD	
96-105	05	1022.00±80.74	37	804.30±150.32	<0.05
106-115	11	1111.80±170.8	88	1003.06±158.32	<0.05
116-125	48	1382.08±145.92	76	1226.57±166.02	<0.05
126-135	51	1769.80±174.79	91	1468.02±221.70	<0.05
136-145	38	2051.57±280.98	74	1763.06±366.89	<0.05
146-155	34	2463.52±295.56	45	2246.66±296.06	<0.05
156-164	25	2989.60±432.65	26	2714.23±460.11	<0.05

Table 10.17 FVC (ml) in Girls

Height (cm)	Control		Affected		P value
	n	Mean ± SD	n	Mean ± SD	
96-105	02	720.00±141.42	26	763.07±134.54	>0.05
106-115	16	1122.50±191.53	80	976.87±158.61	<0.05
116-125	42	1300.20±125.39	76	1178.55±193.67	<0.05
126-135	48	1676.90±252.52	62	1351.98±292.63	<0.05
136-145	38	1983.70±246.54	68	1685.00±233.86	<0.05
146-155	38	2277.90±274.20	40	2022.75±259.72	<0.05
156-164	05	2810.00±429.94	07	2247.14±237.11	<0.05

Table 10.18 FEV_1 (ml) in Boys

Height (cm)	Control		Affected		P value
	n	Mean ± SD	n	Mean ± SD	
96-105	05	900.00±94.07	37	733.78±110.83	<0.05
106-115	11	1042.66±119.20	88	920.22±161.02	<0.05
116-125	48	1261.66±150.59	76	112.89±162.77	<0.05
126-135	51	1573.50±132.37	91	1350.98±183.92	<0.05
136-145	38	1840.00±218.84	74	1681.43±302.68	<0.05
146-155	34	2221.21±290.81	45	2036.22±335.75	<0.05
156-164	25	2676.01±379.37	26	2487.69±460.75	<0.05

Table 10.19 FEV_1 (ml) in Girls

Height (cm)	Control		Affected		P value
	n	Mean ± SD	n	Mean ± SD	
96-105	02	700.00±141.42	26	700.38±113.89	>0.05
106-115	16	1026.90±163.81	80	886.50±136.48	<0.05
116-125	42	1174.80±119.82	76	1072.89±178.51	<0.05
126-135	48	1498.10±209.77	62	1234.70±263.81	<0.05
136-145	38	1837.40±219.29	68	1597.05±246.04	<0.05
146-155	38	2103.90±207.86	40	1913.75±212.55	<0.05
156-164	05	2680.00±345.03	07	2181.40±226.52	<0.05

CONCLUSIONS

Respiratory morbidity rates in 6-15 years old although lower than initial, were higher in affected areas compared with control areas; even 1-1.5 years after the initial study. Similarly, FVC and FEV_1 values were significantly lower in children from affected areas compared with control areas.

Chapter 11

Mental Health Studies in MIC/Toxic Gas Exposed Population at Bhopal

INTRODUCTION

Bhopal gas disaster was the first of its kind in India to be studied systematically for mental health effects. Earlier reports on the mental health impact of disasters were descriptive and related to the cyclones in Andhra Pradesh and Circus tragedy in Bangalore[1]. Bhujanga Rao and Zubair[2] reported that the majority (77.5%) of the studied patients affected by the cyclone in Andhra Pradesh were suffering from neurotic disorder.

Information about the mental health effects of Bhopal disaster are available from a number of sources, some are from general health surveys and others are specific studies on mental health. The direct involvement of the psychiatrists/ neurologists at the field level did not occur till about 8 weeks after the disaster. This delay was in spite of the recognition of the importance of mental health effects of the disaster within the first fortnight of the disaster. By coincidence, the Fourth Advisory Committee on Mental Health of ICMR was meeting on December 12-14, 1984. The experts in the meeting recognized the need of the affected population as follows[3]:

> *"the recent developments at Bhopal involving the exposure of 'normal' human beings to substances toxic to all the exposed and fatal to many, raise a number of mental health needs. The service needs and research can be viewed both in the short-term and long-term perspectives. The acute needs are the understanding and provision of care for confusional states, reactive psychoses, anxiety-depression reactions and grief reactions. Long term needs arise from the following areas, namely, (i) psychological reactions to the acute and chronic disabilities, (ii) psychological problems of the exposed subjects - currently not affected, to the uncertainties of the future, (iii) effects of broken social units on children and adults, and (iv) psychological problems related to rehabilitation".*

An important reason for the delay in starting mental health interventions was the absence of mental health professionals in the state of Madhya Pradesh and the city of Bhopal in 1984. At that point of time, none of the five medical colleges had a psychiatrist on the staff.

General Studies on Mental Health

The initial understanding of the mental health effects arose from studies of general health.

Misra et al[4] reported on 33 adult patients treated during the acute phase at the Medical College Hospital. They found that symptoms of severe cough and dyspnoea were followed by fainting in 55% of the patients. The duration of unconsciousness ranged from 30 minutes to 3 days. One patient who had suffered from prolonged unconsciousness had myoclonic jerks localized to the right upper extremity and generalized hyper-reflexia, suggestive of encephalopathy. Three patients with prolonged unconsciousness and brisk deep tendon jerks had extensor plantar response. Mild to moderate headache (55%), giddiness (46%), burning

sensation in hands and feet (9%) and hypoanaesthesia (3%) were also reported. At the 3 month follow-up of this group of patients, depression and irritability were the commonly reported symptoms.

Gupta et al[5] studied systematically 687 affected persons of various age groups and from different affected areas, two months after the disaster and another 592 persons after the four month period. These studies included "behavioural studies". There was a control population. The behavioural studies were carried out in 350 adults. The psychological tests used were to "detect non-intellecltual personality disturbances, changes in mood, readiness for affective reactions, neuroticism and the dimension of extroversion/introversion. The specific tests administered were digit span test, Benton visual retention test, digit symbol test, Bourdon Wiersma vigilance test, simple reaction time, Santa Ana test, Rorscharch and Eysenck personality inventory. The behavioural tests showed that memory, mainly visual perceptual and attention/response speed along with attention/vigilance were severally affected in the gas-exposed population. Further, statistically significant differences were observed between the control and the exposed groups on all the parameters tested.

> *"The gas exposed groups, especially the females had poor scores in the auditory memory tests. The exposed male group showed significantly low visual memory as compared to controls and females."*

The visual memory was more affected than the auditory memory. Perceptual motor speed was significantly lower in the gas-exposed group. All these changes were associated with subjective complaints of lack of concentration and poor attention. In the manual dexterity tests there were no differences across the groups. The scores on Eysenck Personality Inventory (EPI) showed that 79.6% had poor scores on general liability items, whereas 88.6% with poor scores had a tendency to general fatigue with somatic complains. Only 4.5% had neurotic tendencies. As a group, women were more affected than men and this difference was statistically significant.

Cullinan et al[6] carried out an epidemiological study of a representative gas-exposed population, nine years after the disaster, in January 1994. They studied 474 subjects and a control group. Of this sample, 76 were subjected to detailed neurological testing which included vestibular and peripheral sensory function and tests for short-term memory. In this study a high proportion of subjects reported a wide variety of neuropsychiatric symptoms like abnormal smell, abnormal taste, faintness, headache, difficulty to stay awake and abnormal balance. Headache was reported by 80% of the subjects as compared to 50% in the control population. Neurological examination showed that a high proportion was judged to have clinical evidence of central, peripheral or vestibular neurological disease. The mean short-term memory scores were lowest among those heavily exposed (1.0 vs 3.0). There was some evidence of impaird extrapyramidal functions. There was also abnormal vertical drawing test among the exposed. In this group the psychological symptoms reported were fatigue (88%), anxiety (65%), difficulty in concentration (64%). Difficulty in decision making was reported in 80% as compared to 35% in the control population. Irritability was reported by 33% as compared to none in the control group. There was a consistent gradient across the separate exposure groups for all symptoms except depression. Approximately 25% reported symptoms of depression.

MENTAL HEALTH STUDIES - ADULTS

The initial assessment started in the first week of February 1985 (eight weeks after the disaster). These initial observations led to an estimate of the magnitude of mental health problems of the population at 50% of those in the community and of about 20-30% of those attending the general medical facilities[7].

Immediately following these observations, during February-April 1985, a psychiatric team carried out systematic studies of patients attending the general medical clinics. As a first step, ten general medical clinics in the disaster-affected area were chosen. A team consisting of a psychiatrist, a clinical psychologist, and a social worker visited one clinic a day, by rotation in a randomized fashion, on three occasions and screened all the newly registered adult patients with the help of a psychiatric screening questionnaire namely, self-reporting questionnaire (SRQ)[8]. Subjects identified as probable psychiatric patients were then evaluated in detail by the psychiatrist with the help of a standardized psychiatric interview, the Present State Examination (PSE)[9]. Clinical diagnosis was based on the International Classification of Diseases (9^{th} revision) (ICD-9)[10].

During a period of 3 months (February-May 1985), of the 855 patients screened at the 10 clinics, on the basis of their SRQ scores, 259 were identified as having a potential mental disorder. Of these potentially mentally ill people, 44 could not be evaluated, and 215 were assessed using the PSE. The confirmed number of psychiatric patients was 193, yielding a prevalence rate of 23.6%. Most of the patients were females under 45 years of age (74%). The main diagnostic categories were : anxiety neurosis (25%), depressive neurosis (37%), adjustment reaction with prolonged depression (20%), and adjustment reaction with predominant disturbance of emotions (16%). Cases of psychosis were rare, and they were not related to the disaster[11].

During the same period, in the third month post-disaster, neurological studies were carried out[12]. This was a survey of the gas-affected patients admitted to the various hospitals in the Bhopal City. A total of 129 adults and 47 children were studied for neurological problems. Evidence of involvement of the central nervous system was present in three patients in the form of stroke, encephalopathy and cerebellar ataxia. Involvement of the peripheral nervous system was observed in 6 patients. Vertigo and hearing loss occurred in 4 patients. Many patients reported transitory symptoms like loss of consciousness (50%), muscle weakness, tremors, vertigo, ataxia and easy fatigability. Most of these symptoms cleared up after varying periods of time. Of the 47 gas affected children, loss of consciousness at some time or other occurred in half of the patients. Fits occurred during the course of the illness in 3 children. Mental regression was observed in one child who had commenced speaking in sentences but stopped talking after the disaster. There were no abnormalities in the neurological examination in all of the children. An important observation by the doctors who had examined the children during the early phase of illness was generalized hypotonia and weakness. Two children were noted to be ‘floppy’ with weakness of limb movements and had difficulty in getting up from the ground. Of the 3 patients who had central nervous system involvement, the patient with stroke died. His autopsy showed intense congestion and petechial hemorrhages of the gray and white matter with frank hemorrhage in the circle of Willis area, perhaps indicating the sustained microvascular damage by the circulating toxic gas.

Research Studies

As part of the total medical research involving the Bhopal gas affected population by the Bhopal Gas Disaster Research Centre (BGDRC), two mental health studies and one training intervention were taken up.

The three projects were:

1. Mental health studies in toxic gas exposed population at Bhopal.
2. A pilot psychiatric study of children (0-16 years) affected by the toxic gas.
3. Training programme for medical officers on mental health care of the disaster affected population.

Rationale for the Study

It is unfortunate that at the time of the disaster very little was known about the acute and chronic effects of the toxic gas on general health and more so in regard to its psychological sequelae. It was, however, reasonable to assume that this disaster would probably result in emotional as well as physical problems in the affected population and may even affect future generations to come. It was felt therefore mandatory that the toxic gas exposed population be studied for their mental health status and which may ultimately help us to evolve strategies to control the same.

General Objectives

- To study prevalence of psychiatric disorders in toxic gas exposed and non-exposed areas
- To study the factors associated with psychiatric disorders
- To study the course and outcome of disease in identified cases (at first survey) and
- To carry out annual rotational (2^{nd}, 3^{rd}, 4^{th} and 5^{th} year) prevalence surveys on independently drawn samples.

Specific Objectives

To compare the prevalence of psychiatric disorders in severe/moderately exposed areas and non-exposed control areas.

To study the change in prevalence of psychiatric disorders in gas affected and control areas over a period of time.

To study the association of the following factors with the prevalence of mental disorders : age, sex, economic status, degree of exposure to toxic gas, occupation, bereavement, physical status (illness, disability), drug intake habit and family set-up.

To study the degree of recovery, releases in identified subjects suffering from various psychiatric disorders.

To find out if the course and outcome of these disorders bear any relationship to acceptance or non-acceptance of treatment.

METHODS

The design of the study was ex-post facto inquiry. The study involved the assessment of a random sample of the population annually for the prevalence and course of the mental disorders. The staff were trained by the experts to administer mental health item sheet of Verghese and Beig[13]. The psychiatrists/psychologists were trained to administer Present State Examination (PSE). The inter-rater reliability between investigators were also tested from time to time to ascertain the reliability of data.

Selection of Population

A random sample of 700 families from each area, i.e. severely exposed area, mildly exposed area and control area, were surveyed, for each rotational survey independently. This random sample was given by the computer center of the Bhopal Gas Disaster Research Centre (BGDRC), Bhopal from its cohort.

The head of the selected families was approached by the research team. The team comprised of psychiatrist, psychologist, sociologist and a social worker. The mental health item sheet[13] was administered to the head of the family as well as information on the same schedule, regarding other adult members of the family (aged 16+) was collected. If any member of the family was rated positive on three or more items, that individual was further examined in detail. A semi-structured proforma regarding psychiatric history, personal history, pre-morbid personality, etc. was also completed. Subjects diagnosed as having psychiatric problems were assessed using the PSE and they were referred to psychiatrist of Hamidia Hospital, Bhopal for further care. The inter-rater reliability was also tested. Locked houses were revisited twice. Migrated, families, locked houses (even after three visits) were replaced by additional families. The list of additional families was obtained from computer section of BGDRC on random sampling basis.

RESULTS

Prevalence of Mental Disorders

The survey found that there was a 5 fold increase in the prevalence of psychiatric disorders in the severely exposed population as compared to the control population (Table 11.1). The group with mild exposure fell in between the two groups. This is striking in that the control population was not a true control, as in current understanding the population of the whole city of Bhopal would be considered disaster affected population. The differences in the prevalence rates continued throughout the 5 years of the study period in each of the annual surveys. There was gradual decrease in the prevalence rates over the years. The gas exposed population had three times more prevalence of mental disorders as compared to controls at the end of 5 years of the disaster.

Table 11.1 Year-wise Prevalence Rates of Psychiatric Cases

Gender	Exposed						Non-exposed		
	Severe			Mild			Control		
	Population screened	Positive cases	Prev/ 1000	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000
1985-86	1617	221	136.7	1687	136	80.6	1673	46	27.5
1986-87	2007	121	60.3	2198	93	42.3	1613	26	16.1
1987-88	2012	89	44.2	2287	86	37.6	1656	28	16.9
1988-89	2077	101	48.6	2101	107	50.9	1733	26	15.0

Gender Distribution (Table 11.2)

It was found that the prevalence of psychiatric disorders was higher in the females in comparison to males. A similar finding has been observed in exposed and non-exposed areas and also during the rotational surveys. This higher prevalence in females in such disasters is reported in all the world literature.

Table 11.2 Year-wise Distribution of Psychiatric Cases with Respect to Gender, Prevalence Rates per 1000 Population

Gender	Exposed						Non-exposed		
	Severe			Mild			Control		
	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000
1985-86									
Male	868	65	74.9	865	41	47.4	890	19	21.3
Female	749	156	208.3	822	95	115.6	781	27	34.6
1986-87									
Male	1030	32	31.1	1131	20	17.7	850	13	15.3
Female	976	89	91.2	1068	74	69.3	772	13	16.8
1987-88									
Male	1076	26	24.2	1182	19	16.1	912	10	10.9
Female	935	63	67.4	1108	67	60.5	755	18	23.8
1988-89									
Male	1109	23	20.7	1064	18	16.9	941	7	7.4
Female	967	78	80.7	1041	89	85.5	801	19	23.7

Income Status and Mental Disorders

Table 11.3 shows that in the initial survey people belonging to lower income group (per capita income less than Rs.50/- per month) had highest prevalence rate of psychiatric disorders (269.2/1000). It might be because of adverse effects on the physical health of people due to inhalation of toxic gas. It is possible that the affected people were unable to do their work and their household expenditure was based on their daily earning. They were unable to help their family because of ill health. It may be a possible reason for the emergence of psychiatric disorders. On the basis of interaction in the field it was experienced that after the gas leak all possible treatment and other measures were taken by most of the people of higher income group. It was also observed that if financial means were limited and people were helpless in coping with the existing problems, it created tension, anxiety or depression in the person.

Table 11.3 Year-wise Distribution of Psychiatric Cases with Respect to Income: Prevalence Rates per 1000 Population

Income	Exposed						Non-exposed		
	Severe			Mild			Control		
	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000
1985-86									
- <50	130	35	269.2	116	18	155.2	69	3	43.5
50-150	1160	148	126.7	1125	97	86.2	841	20	23.8
150-250	242	28	107.4	300	14	46.7	471	14	29.7
250-350	46	5	108.7	71	4	56.3	141	4	28.4
350- >	31	7	225.8	75	3	40.0	151	5	33.1
1986-87									
- <50	114	5	43.8	109	4	36.7	80	1	12.5
50-150	1507	100	66.3	1536	73	87.5	899	16	17.8
150-250	270	8	29.6	397	13	32.7	365	6	16.4
250-350	69	2	28.9	76	3	39.5	110	1	9.1
350- >	47	6	127.6	80	0	-	159	2	12.6
1987-88									
- <50	107	0	-	122	4	32.8	69	2	28.9
50-150	1482	73	49.2	1515	60	39.6	1100	22	20.0
150-250	309	12	38.8	471	12	25.5	296	4	13.5
250-350	69	1	14.5	74	6	81.1	91	0	-
350- >	45	3	66.7	105	4	38.1	100	0	-
1988-89									
- <50	144	10	69.4	116	6	51.7	57	0	-
50-150	1560	82	52.6	1526	82	53.7	1204	16	13.3
150-250	267	7	26.2	312	13	41.7	322	7	21.7
250-350	50	0	-	103	4	38.8	55	1	18.2
350- >	56	2	35.7	44	2	45.4	95	2	21.1

It was also seen that psychiatric morbidity rates were higher among the higher income group during first and second rotational survey, however in the final rotational survey majority of cases fell in lower income group. The prevalence rate of psychiatric morbidity was lower in higher income group during third rotational survey, probably because the people of this group took treatment which could include the services of a psychiatrist. However, people belonging to lower income group were not aware about the psychiatric disorders. They probably focused their treatment only on physical illness.

Religion

The distribution and comparison was possible between people belonging to Hindu and Muslim religions (Table 11.4). The numbers in other religions were too small for interpretation. The psychiatric morbidity found was higher among the Muslims in comparison to Hindus. The prevalence rate of psychiatric disorders during almost every rotational survey was higher among Muslims than Hindus. This trend was also apparent in the non-exposed area.

Table 11.4 Year-wise Distribution of Psychiatric Cases with Respect to Religion : Prevalence Rates per 1000 Population

Religion	Severe			Mild			Control		
	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000
1985-86									
Hindu	1032	128	124.0	671	37	55.1	1541	40	25.9
Muslim	564	90	159.0	1003	97	96.7	123	6	48.8
Christian	5	0	-	11	1	90.9	2	0	-
Sikh	16	3	187.5	2	1	500.0	6	0	-
Others	-	-	-	-	-	-	-	-	-
1986-87									
Hindu	1240	60	48.4	818	35	42.8	1483	16	10.8
Muslim	724	60	82.9	1363	59	43.3	111	9	81.1
Christian	5	0	-	17	0	-	18	0	-
Sikh	27	1	37.0	2	0	-	10	1	100.0
Others	10	0	-	-	-	-	-	-	-
1987-88									
Hindu	1174	51	43.4	1033	26	25.2	1503	22	14.6
Muslim	788	34	42.7	1232	59	47.9	157	4	25.5
Christian	4	1	250.0	19	1	52.6	2	1	500.0
Sikh	34	2	58.8	4	0	-	5	1	200.0
Others	3	0	-	2	0	-	-	-	-
1988-89									
Hindu	1223	1	41.7	863	36	41.7	1611	21	13.0
Muslim	812	47	57.9	1222	71	58.1	120	4	33.3
Christian	4	0	-	14	0	-	2	0	-
Sikh	34	3	88.2	3	0	-	9	1	111.1
Others	3	0	-	2	0	-	-	-	-

Age Distribution

Psychiatric morbidity when studied with age, it was noticed that the prevalence rate of psychiatric disorders were higher among the persons belonging to less than 16 years age or more than 26 years (Table 11.5). This trend was observed during the initial survey and in all rotational surveys and also in the exposed and non-exposed areas.

The prevalence rate of psychiatric disorders in the exposed area during initial survey was higher among the age group of 36-45 years (166.1/1000) followed by 45-55 years (158.4/1000) and 26-35 years (134.3/1000). Although not consistent in a particular age group during different rotational surveys, the results revealed that this was higher among the middle aged

Table 11.5 Year-wise Distribution of Psychiatric Cases with Respect to Age : Prevalence Rates per 1000 Population

Age	Exposed						Non-exposed		
	Severe			Mild			Control		
	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000	Population screened	Positive cases	Prev./ 1000
1985-86									
- < 16	46	4	86.9	27	2	74.1	53	1	18.9
16-25	555	35	63.1	677	24	35.4	593	5	8.4
26-35	473	83	175.5	458	42	91.7	549	20	36.4
36-45	240	48	200.0	235	31	131.9	281	13	46.3
46-55	154	28	181.8	149	20	134.2	115	5	43.5
56-65	105	16	152.4	90	12	133.3	55	2	43.5
65 - >	44	7	159.1	51	5	98.0	25	0	-
1986-87									
- < 16	29	2	68.9	44	0	-	47	1	21.3
16-25	806	27	33.5	875	19	21.7	634	7	11
26-35	514	48	93.4	609	38	62.4	507	9	17.7
36-45	318	21	66.0	324	20	61.7	253	4	15.8
46-55	178	10	56.2	178	9	50.6	93	2	21.5
56-65	112	10	89.3	109	7	64.2	63	1	15.9
65 - >	50	3	60.0	61	1	16.4	25	2	80.0
1987-88									
- < 16	49	3	61.2	42	0	-	46	1	21.7
16-25	789	14	17.7	974	25	25.7	657	2	3.0
26-35	502	24	47.8	600	24	40.0	557	14	25.1
36-45	330	29	87.9	319	18	56.4	228	6	26.3
46-55	203	14	68.9	187	12	64.2	103	4	38.8
56-65	105	5	47.6	110	5	45.4	52	1	19.2
65 - >	34	0	-	58	2	34.5	24	0	-
1988-89									
- < 16	31	0	-	42	0	-	35	0	-
16-25	895	28	31.3	845	16	18.9	718	6	8.3
26-35	544	23	42.3	576	31	53.8	537	10	18.6
36-45	290	31	106.9	322	31	96.3	240	6	25.0
46-55	173	13	75.1	188	24	127.7	128	3	23.4
56-65	100	4	40	95	5	52.6	57	1	17.5
65 - >	44	2	45.4	37	0	-	27	0	-

Follow-Up of the Psychiatric Patients

Table 11.6 shows the follow-up of patients from initial to 5th follow-up.

Table 11.6 Comparative Statement of Patients Since Initial Survey to Fifth Follow-up

Year	Exposed area				Non-exposed area	
	Severe	Drop out	Mild	Drop out	Control	Drop out
1985-86	279		148		47	-
1986-87	230	49	132	16	42	5
1987-88	211*	20	122@	11	42	-
1988-89	192	19	114	7	41	-
1989-90	177	15	104	10	39	2
1990-91	184	13	97	7	39	-
1991-92*	160+	3	61**	9	-	***

Drop out cases include deaths and migration

* upto 31st March, 92

** Upto 31st March 1992 there were 70 cases due for follow up among them 61 were followed up, 8 were migrated and one died

*** All the cases in control area were due after 31st March. It is therefore not included in the report

@One case in the mild area from the migrated group above, turned up during 3rd and 4th follow up

\+ One case were followed up after 31st March

Diagnosis of Psychiatric Patients in Final Follow-UP

The diagnostic break-up of 5th follow-up survey is given in Table 11.7. It can be seen that the largest number were of neurotic depression followed by anxiety state etc., more in the severely affected area than in the mildly affected.

Table 11.7 Diagnostic Break-up of Fifth Follow-up

	Severe n = 164	Mild n = 97	Control n = 39
Anxiety state	40	29	06
Neurotic depression	50	42	10
Hysteria	05	02	-
M.D.P	01	03	-
Schizophrenia	02	03	02
Mental retardation	-	-	02
Dementia	-	01	-
Recovered	64	17	18
Other neurosis	02	-	01

DISCUSSION

The mean prevalence rate of psychiatric morbidity is about four times higher in the exposed area in comparison to non-exposed area. This difference was somewhat lower during the second rotational survey. Of the other variables studied, education had no significant effect upon the psychiatric morbidity. The psychiatric disorders were almost equally distributed in different levels of education. Similar trend was observed in every rotational surveys and also in exposed and non-exposed areas.

Psychiatric morbidity with regard to occupation, it was observed that the prevalence rate was higher (203.9/1000) among the housewives in the exposed area. No other occupational group was significantly associated with psychiatric morbidity. The psychiatric morbidity was almost equally distributed in the different occupational levels.

The results showed that leakage of toxic gas was an important factor for emergence of psychiatric disorders. On the basis of results obtained during initial survey, it was observed that the prevalence rate of psychiatric disorders was higher among those persons who were

present in their houses on the night of gas leakage. The prevalence rate in the severely exposed area was 139.2/1000 and in the mildly exposed area 80.8/1000, whereas, in non-exposed area it was 26.8/1000.

Similarly, the people who were sleeping outside their houses had higher prevalence rate of psychiatric morbidity (145.8/1000) in comparison to those people who were inside the house (108.5/1000). In other words it can be stated that persons who were outside their house on the night of the gas leakage inhaled more MIC gas and had higher prevalence rate of psychiatric morbidity.

Remission of Symptoms

During first, second, third and fourth follow-up the percentage of patients in continuous illness were 89.6%, 66.8%, 56.8% and 47.4% respectively. On the other hand rate of recovery gradually increased from 3.04% to 38.9%. Remission of symptoms was not present in majority of patients during the first follow-up and it gradually came down in the fourth follow-up. It is interesting to mention here that majority of patients (58.3%) took treatment for psychiatric disorders from general physician during first follow-up. During second, third and fourth follow-up it was 51.7%, 49.5%, 53.1% respectively. Whereas 37.4% patients did not take treatment from any source at the time of follow-up. The rate of recovery also increased gradually in the mildly exposed area and in non-exposed area. In the mildly exposed area it increased from 7.6% to 44.4% and in non-exposed area from 14.3% to 36.6%.

Limitations of the Study

Looking back, the epidemiological study had a number of limitations, all of these contributing to relative low estimates of the mental disorders. These are: (i) use of head of household as informant rather than the individual; (ii) the Verghese and Baig[13] check list instead of a instrument like SRQ; (iii) the control population being from Bhopal city; and the (iv) lack of record of the treatment taken by the patients and the course of the mental disorders. However, both in terms of it being the first major study of psychiatric problems in a disaster survivor population as well as the large scale study over 5 years, the study forms an important milestone in the field of disaster mental health care.

II. PILOT PSYCHIATRIC STUDY OF CHILDREN (0-16 YEARS)

The aim of the study was to compare the frequency and type of psychiatric disorders and intellectual levels of children (0-16 years) of 100 families (having at least one child between 0-16 years) randomly selected from one area severely affected by toxic gas and 100 families (having at least one child between 0-16 years) from the control area.

The data collection was done in two phases. In phase one, a special screening instrument Psychiatric Symptom Screening Schedule (PSSS) was constructed. This was based on the earlier instrument developed for the Vellore study[15]. Following the construction, the research staff were trained to establish inter-rater reliability for PSSS and the use of the multi-axial child psychiatric diagnosis. In the phase two, the collection of data was carried out using the epidemiological data base to select the 100 experimental and control families. Each family was interviewed using the PSSS and those found positive were individually evaluated by a psychiatrist to arrive at a psychiatric diagnosis. Psychological tests for intellectual level were administered to all the children.

RESULTS

One outcome of the study has been the developmental of psychiatric symptom screening schedule (PSSS) which can identify children with moderate to severe psychiatric disorders in general population. 100 families each studied of affected and control areas yielded 252 and 241 children respectively. Children in exposed and control area in terms of age distribution (0-5, 6-10 and 11-16 years), sex and income were comparable.

The rate of psychiatric disorders in exposed area was 12.66% as compared to 2.4% in the control area. The difference was statistically significant (Table 11.8).

Table 11.8 Frequency of Psychiatric Disorders in the Children of Affected and Control Areas

	Affected Area	Control Area
Number of families studied	100	100
Number of children screened	252	241
Children rated positive on PASS	35(13.88%)	6(2.4%)
Number of children diagnosed on multiaxial classification (Axis.I, II, III	32(12.66%)	6 (2.4%)

The rate of psychiatric disorders in the affected area was approximately over 5 times than that in the control area. Enuresis, unsocialised disturbance of conduct, specific developmental delay in speech and mental retardation were the most common psychiatric disorders seen in the exposed group (5.6%, 3.6% and 1.6% respectively) (Table 11.9).

Table 11.9 Frequency of Symptoms on PSSS

Symptoms	Affected Area (n=252)		Control Area (n=241)		X^2	Statistical significance
	N	%	N	%		
Enuresis/encopreasis	14	5.55	1	1.65	6.77	S
Disobedient/stubborn	11	4.36	1	.41	8.32	S
Tremor tentrum	11	4.36	1	.41	8.32	S
Mental retardation	6	2.3	-	-	6.00	S
Delayed/poor development of speech	5	1.98	-	-	5.00	S
Aggressive	3	1.19	-	-	3.00	NS
Irritability	3	1.19	-	-	3.00	NS
Headache	2	.79	-	-	2.00	NS
Fits	1	.39	-	-	1.00	NS
Scholastic	1	.39	-	-	1.00	NS
Truancy/irregular to school	1	.39	-	-	1.00	NS
Gross neglect of personal hygiene	1	.39	-	-	1.00	NS
Shyness	1	.39	-	-	1.00	NS
Pica	1	.39	-	-	1.00	NS

S = Significant NS = Not significant

The commonest symptoms in both the affected and control areas were enuresis/encopresis; disobedient/ stubborn and temper tantrums. The prevalence rate were higher in the exposed group as compared to the control families. In two cases (out of a total 14 cases) of enuresis started more than one year after gas exposure, in 5 cases it started soon after the disaster and in 7 cases enuresis was present before the disaster. In 5 conduct disorders (out of total of 9 cases of conduct disorder) the problem started within two months of the disaster.

As regards the intellectual levels the difference in exposed and control area was seen in the age group of 6 to 16 years where it was found that the children in the exposed area had significantly lower intellectual levels than the control area (Tables 11.10 to 11.12).

Table 11.10 Comparison of Intellectual Levels (in percentiles) in the Affected and Control Areas in 6-10 Years Age Group, as Assessed by Coloured Progressive Matricees

Percentiles Z Value	Affected Area N = 118	Control Area N = 105
25^{th} to 50^{th} 12.0 (S) (91-100)	5 (4.2%)	21.9%
10^{th} to 25^{th} 5.13 (S) (81-90)	11 (9.3%)	18 (17.14%)
5^{th} to 10^{th} 9.61 (S) (75-80)	101 (85.5%)	65 (60.95%)
Below 5^{th} percentile	02 (1.69%)	

$X^2 = 22.77$ df = 3, P<.001

Table 11.11 Comparison of Intellectual Levels (in percentiles) in the Affected and Control Areas in 11-16 Years Age Group, as Assessed by Coloured Progressive and Standard Progressive Matricees

Percentiles Z Value	Affected area N = 118	Control area N = 105
25^{th} to 50^{th} 10.3 (S) (91-100)	3 (4.34%)	21 (27.6%)
10^{th} to 25^{th} 2.76 (S) (81-90)	8 (11.59%)	10 (13.15%)
5^{th} to 10^{th} 0.57 (S) (75-80)	55 (79.7%)	45 (59.2%)
Below 74	03 (4.3%)	

$X^2 = 17.42$ df = 3, P<.001

Table 11.12 Comparison of Approximate IQ of the Children (up to 16 years) in the Affected and Control Areas

I.Q. (approximate)* categories	Control area N = 241	Affected area N = 252
91 to 100	17 (7.05%)	7 (2.8%)
81 to 90	129 (53.5%)	84 (33.3%)
75 to 80	95 (39.4%)	156 (61.9%)
50 to 74		5 (1.98%)

*IQ Scores are derived from D.Qs (assumed to be equal to Iqs) and percentiles. These are therefore approximation only. It can be seen that fewer (36.1%) children of the affected area are in the IQ range 81-100 than those in the control area (60.55%). Overall, the children from the affected area have lower intellectual levels than those from the control area. This trend was not clear cut in the age group upto 5 years. This may be because all the children in this age group could not be administered any one test, except VSMS. When the intellectual levels of the entire group of children in the exposed and control area were compared there was a trend towards the children from the exposed area to have lower intellectual levels than the children from the control area.

The overall results of this study showed that the children in gas affected area had much higher rates of psychiatric disorders and lower intellectual levels as compared to children in the control area. The increase in psychiatric disorders in exposed area compared well with the findings of adult toxic gas study.

SUMMARY

A marked difference was found in the rate of psychiatric morbidity in the affected and the control areas. The psychiatric symptom screening schedule identified 35 cases in the affected area. Out of these 35, 32 (12.66%) were given a psychiatric diagnosis. Enuresis was the commonest diagnosis, found in 14 cases. In 5 cases it started after the disaster. 9 cases were given the diagnosis of unsocialised disturbance of conduct. 4 cases each of mental retardation and specific developmental delay in speech were also found in the affected area. In one case, the diagnosis of psychalgia was given.

III. TRAINING OF MEDICAL OFFICERS IN MENTAL HEALTH CARE IN BHOPAL

One of the challenges faced by the team of psychiatrists was the provision of psychiatric services to the affected population. For a total population of 8000000 and the affected population of about 200000, there was no psychiatric help available in the city. A number of measures were taken to meet this challenge. **Firstly,** the senior psychiatrists worked to prepare clinical vignettes of patients to sensitize the medical professionals and the administrators. Because of the issues of compensation, majority of the administrators and medical professionals considered that the complaints, especially the psychiatric symptoms were imaginary and compensation-related. This misconception was corrected by demonstrating the real nature of the symptoms and the universality of after-effects of the disaster on the mental health of the affected population. **Secondly,** starting from February 1985, teams of psychiatrists, clinical psychologists, psychiatric social workers from Lucknow were located in the city for period of 2-4 weeks to provide psychiatric care to the affected population. This was a short-term measure (11). **Thirdly,** adequate measure was taken up to train the general medical officers working with the affected population with the essential skills of mental health care. This was indeed very challenging but was a rapid way of increasing the mental health care in the city. Soon after the disaster, additional medical officers were moved to the city and located in the different gas affected areas to provide general medical care to the population. In April 1985, about 50 medical officers were working in the various health facilities in the gas affected areas. Most of the doctors had no training in mental health as part of their initial medical training, as there were no teachers of psychiatry in the State medical colleges. This lack of training was reflected in their poor perception of the emotional needs of the disaster-affected population. The basic orientation of these doctors was highly biological.

CONCLUSIONS

Disasters are a challenge every where for the affected populations as well as the professionals. However, they represent special challenges and opportunities in developing countries. Bhopal disaster is a milestone in understanding the mental health aspects of disasters. The research has shown the high physical and mental morbidity in the general population and the continuing need for longitudinal health studies. Using a public health approach in priority setting, identification of interventions and training of existing personnel, utilizing the community resources the mental health needs of the survivors of disasters can be addressed.

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Chapter 12

Follow Up Study of Ocular Changes in MIC/Toxic Gas Exposed Population of Bhopal on Long Term Basis

INTRODUCTION

Almost all exposees to MIC/toxic gas suffered from minor or major eye as well as respiratory ailments. While the respiratory morbidities are described elsewhere, eye morbidities are described in this chapter.

Acute Phase Management

Exposure to MIC/toxic gas instantly produced eye symptoms, viz., foreign body sensation, burning, excessive lacrimation, photophobia, difficulty in keeping eyes open and blurring of vision. On detailed examination, 60 to 70% of the patients had both conjunctival and circumcorneal congestion with relatively little oedema. A fair number of cases had superficial corneal ulcers, mostly involving the central zone and interpalpebral region (Figs. 12.1 and 12.2). A mild flare with constricted pupils, sluggishly reacting to light could be seen in a few cases. Fundus was essentially normal except in a few cases who showed oedema and superficial hemorrhages in retina, probably due to hypoxia.

The treatment mainly consisted of appropriately washing the eyes, application of antibiotic ointment, dilating pupils with atropine wherever indicated. This regimen produced dramatic results within a few days.

However, as the gas was found to be extremely toxic and reactive and its long term effects on human health were unknown, it was feared that a large number of the exposees may become blind. Therefore, long term epidemiological studies were instituted by the Indian Council of Medical Research, New Delhi. Also, detailed clinical follow up of these patients was undertaken.

Long Term Ocular Follow Up Studies (1985-92)

The long term clinical follow up studies on ocular morbidities were conducted in two phases:

PHASE I: From March 1985 to August 1988

PHASE II: From September 1988 to September 1992

Specific Objectives

1. To estimate the prevalence rates/incidence of specific ocular morbidities by conducting annual surveys.
2. In-depth studies to determine the extent of morbidities, by doing detailed examination of the anterior and posterior segments.

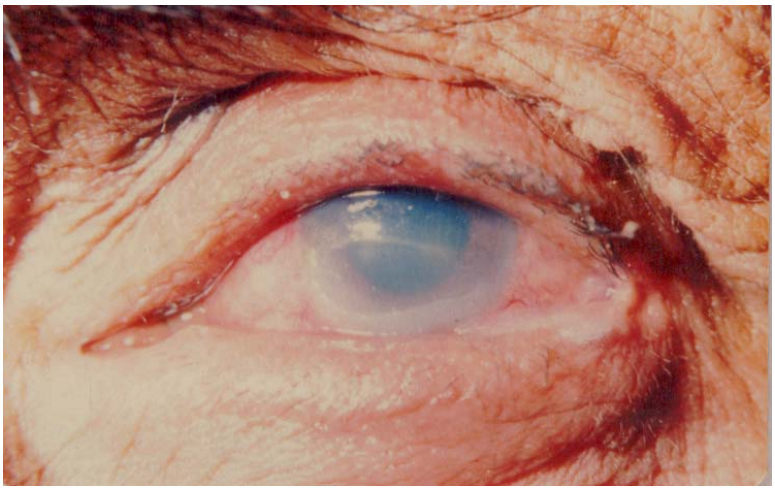

Fig. 12.1 Acute phase corneal ulcer (inferior segment) with circumciliary congestion

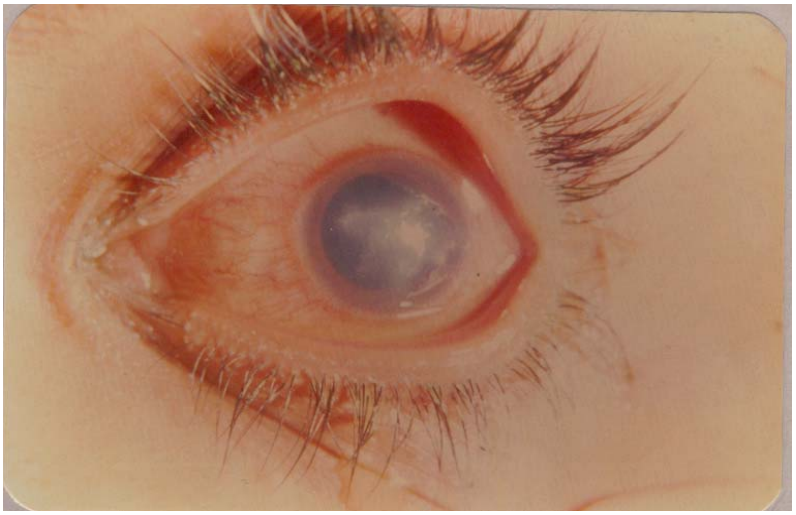

Fig. 12.2 Corneal ulcer with circumcorneal congestion

Anterior Segment

The effect of toxic gas on the following was investigated:

1. Visual acuity
2. Conjunctiva – epithelium and goblet cells
3. Tears – secretion and chemical composition
4. Corneal specular microscopic endothelium study
5. Lens – to study any cataractous changes in various age groups
6. Ocular motor system involvement

Posterior Segment

To study any structural changes in the following by ophthalmoscopy

1. Retina
2. Optic nerve
3. Electrophysiological changes with ERG and EOG equipment

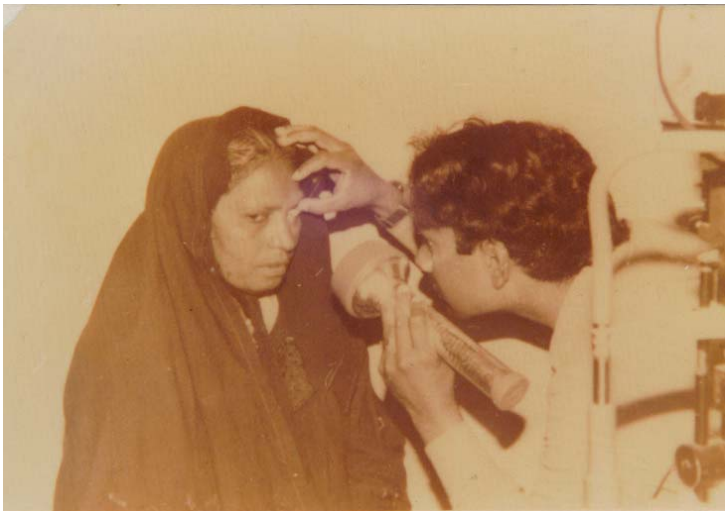

Fig. 12.3 Routine eye examination at a field centre

Fig. 12.4 Slit lamp examination at a field screening centre

PHASE I STUDY (March 1985 to August 1988)

MATERIAL AND METHODS

A study sample of 9465 subjects and a control sample of 3710 subjects for comparison were randomly drawn from the ICMR baseline cohorts registered from the exposed/affected and unexposed/control areas respectively, for long term epidemiological studies.

These subjects were contacted by home visits by a team of Medical Officer and two field assistants. The cases were examined in the field with torch (Fig. 12.3) and classified into the following categories:

1. Normal (Code II) – No eye abnormality detected in the field.
2. Abnormal (Code I) – Corneal or lenticular opacities as detected with torch or had chronic conjunctivitis.

All code I cases were referred to Comprehensive Care Unit (CCU) which was located initially in the ophthalmology unit of Gandhi Medical College, Bhopal, but later (January 1987) shifted to each of the field areas, to improve compliance for follow-up. Then, a temporary clinic was set up in each locality where field work was being done. The slit lamp and ophthalmoscope were kept in that clinic, and detailed examination of cases referred from the field units was done then and there only (Fig. 12.4). This reduced the percentage drop-out of the patients from 35% to about 17%.

Code III cases. It was soon realized that by simple examination with torch, in the field, some cases of superficial corneal opacities were being missed. It was therefore decided that 50% of the code II so called normal cases would also be referred to CCU for detailed examination.

It may be noted that the lenticular opacities and chronic conjunctivitis were taken as toxic gas related abnormalities. Specular microscopy was also done in a few cases to detect quantitative and qualitative changes in the corneal endothelium to assess further corneal decompensation.

A similar methodology was adopted for control areas.

Statistical analysis of data. The data collected from the exposed and control areas were compared, using the test of proportions (Z test).

OBSERVATIONS AND DISCUSSION

On the basis of clinical history and symptomatology, the study sample was stratified into 4 categories (Table 12.1). It can be seen that in each of the four strata, approximately 59 to 88% of the sample could be covered. The latter (5744) constituted 7.6% of the ICMR registered cohort comprising 75976 subjects. Similarly, in the control sample 1710 persons, i.e., 46% of the total 3710 were covered.

Table 12.1 Stratification Categories of Registered Cohort and Study Sample

Category	Criteria	Cohort 85	Sample	Studied Phase I
I	Persons who had immediate effect and/or developed ophthalmic symptoms later and were still suffering	8,637	6,652	3,903 (58.7%)
II	Persons who had immediate and/or later effect but presently not suffering	55,278	1,759	1,145 (65.1%)
III	Immediately affected and had later effect with recurrent attacks of ophthalmic illness	12,036	1,046	689 (65.9%)
IV	No immediate effect, only later effects	25	8	7 (87.5%)
Total		75,976	9,465	5,744 (60.7%)

The study sample was found similar to the ICMR baseline cohort in respect of age, gender, literacy status, religion etc. In strata IV, however, the number of subjects was too small; the comparison may not be therefore valid. Furthermore, smoking habits, alcohol consumption and tobacco chewing also showed similar patterns.

Ocular Morbidities

Trachoma and chronic irritative conjunctivitis. The prevalence rates of both trachoma (Table 12.2) and chronic irritative conjunctivitis (Fig. 12.5 and Table 12.3) in the exposed

population were significantly higher ($p<0.01$) when compared with the control/unexposed population when all age groups and strata were considered together ($p<0.01$). There was no significant difference between age groups or between the stratified categories. It may be noted that the prevalence rates of both conditions increased with age.

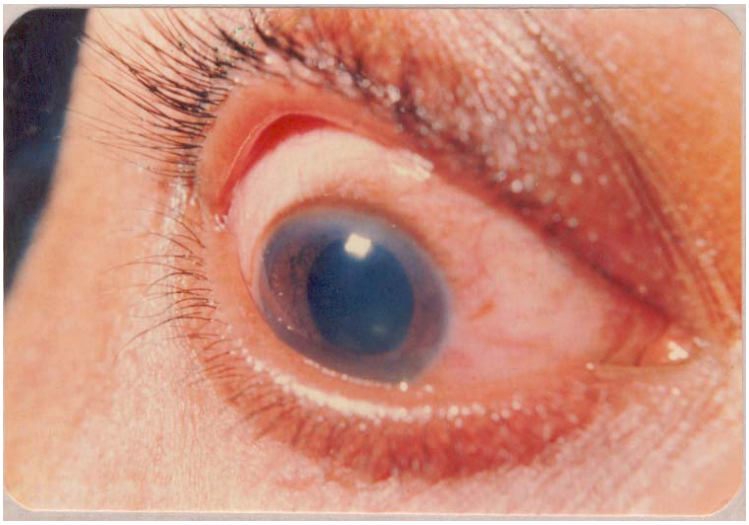

Fig. 12.5 Chronic irritative conjunctivitis

Table 12.2 Prevalence Rates of Trachoma in Various Age Groups of Exposed and Control Population

Age groups	**0-14**		**15-29**		**30-44**		**45-59**		**>60**		**Total**	
Exposed strata	**T**	**P**	**T**	**P**	**T**	**P**	**T**	**P**	**T**	**P**	**T**	**P**
I	13 (1.5)	897	72 (7.0)	1023	254 (30.2)	840	262 (40.3)	651	251 (51.4)	488	852 (21.9)	3899
II	8 (2.3)	349	34 (9.7)	350	72 (28.5)	253	57 (41.9)	136	28 (53.9)	52	199 (17.5)	1140
III	9 (5.2)	174	26 (11.5)	226	47 (27.7)	170	42 (53.9)	78	20 (52.6)	38	144 (21.0)	686
IV	-	4	-	1	-	1	1 (100)	1	-	-	1 (14.3)	7
Total exposed	30 (2.1)	1424	132 (8.3)	1600	373 (29.5)	1264	362 (41.8)	866	299 (51.7)	578	1196 (20.9)*	5732
Controls	10 (1.5)	664	47 (11.8)	400	89 (29.2)	305	42 (51.2)	82	18 (58.1)	31	206 (13.9)	1482

T = No. of cases with active or healed trachoma
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, $p<0.01$ (Z test)

Table 12.3 Prevalence Rates of Chronic Irritative Conjunctivitis in Various Age Groups of Exposed and Control Population

Age groups	0-14		15-29		30-44		45-59		>60		Total	
Exposed strata	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	C	P
I	149 (16.6)	897	281 (27.5)	1023	383 (45.6)	840	340 (52.2)	651	220 (45.1)	488	1373 (35.2)	3899
II	60 (17.2)	349	122 (34.9)	350	128 (50.6)	253	77 (56.6)	136	26 (50.0)	52	413 (36.2)	1140
III	34 (19.5)	174	74 (32.7)	226	79 (46.5)	170	37 (47.4)	78	20 (52.6)	38	244 (35.6)	686
IV	1 (25)	4	1 (100)	1	1 (100)	1	0	1	0	0	3 (42.9)	7
Total exposed	244 (17.1)	1424	478 (29.9)	1600	591 (46.8)	1264	454 (52.4)	866	266 (46.0)	578	2033 (35.5)*	5732
Controls	73 (11.0)	664	100 (25)	400	147 (48.2)	305	43 (52.4)	82	16 (51.6)	31	379 (25.6)	1482

C = No. of cases with irritative conjunctivitis
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, p<0.01 (Z test)

The findings were suggestive of people in the exposed areas running away from homes, trying to keep their eyes open.

Conjunctival xerosis. Table 12.4 shows that the prevalence rates of conjunctival xerosis were significantly higher in the control group as compared with the exposed group (p=<0.01), in all age groups.

Table 12.4 Prevalence Rates of Conjunctival Xerosis in Various Age Groups of Exposed and Control Population

Age groups	0-14		15-29		30-44		45-59		>60		Total	
Exposed strata	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
I	24 (2.7)	897	14 (1.4)	1023	10 (1.2)	840	6 (0.9)	651	1 (0.2)	488	55 (1.4)	3899
II	5 (1.4)	349	6 (1.7)	350	2 (0.8)	253	2 (1.5)	136	-	52	15 (1.3)	1140
III	4 (2.3)	174	8 (3.5)	226	2 (1.2)	170	-	78	-	38	14 (2.0)	686
IV	-	4	-	1	-	1	-	1	-	-	-	7
Total exposed	33 (2.3)	1424	28 (1.8)	1600	14 (1.1)	1264	8 (0.9)	866	1 (0.2)	578	84 (1.5)*	5732
Controls	27 (4.1)	664	9 (2.3)	400	4 (1.3)	305	2 (2.4)	82	2 (6.5)	31	44 (3.0)	1482

C = No. of cases with conjunctival xerosis
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, p<0.01 (Z test)

Table 12.5 Corneal Involvement in Various Age Groups of Exposed and Control Population

Age groups	0-14		15-29		30-44		45-59		>60		Total	
Exposed strata	C	P	C	P	C	P	C	P	C	P	C	P
I	46 (5.1)	897	106 (10.4)	1023	179 (21.3)	840	159 (24.4)	651	152 (31.2)	488	642 (16.5)	3899
II	11 (3.2)	349	34 (9.7)	350	39 (15.4)	253	30 (22.1)	136	21 (40.4)	52	135 (11.8)	1140
III	7 (4.0)	174	22 (9.7)	226	44 (25.9)	170	31 (39.7)	78	19 (50.0)	38	123 (17.9)	686
IV	-	4	-	1	-	1	-	1	-	-	-	7
Total exposed	64 (4.5)	1424	162 (10.1)	1600	262 (20.7)	1264	220 (25.4)	866	192 (33.2)	578	900 (15.7)*	5732
Controls	3 (0.5)	664	13 (3.3)	400	37 (12.1)	305	16 (19.5)	82	9 (29.0)	31	78 (5.3)	1482

C = No. of cases with corneal involvement
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, $p<0.01$ (Z test)

Table 12.6 Corneal Opacity in Various Age Groups of Exposed and Control Population

Age groups	0-14		15-29		30-44		45-59		>60		Total	
Exposed strata	CO	P	CO	P	CO	P	CO	P	CO	P	CO	P
I	37 (4.1)	897	100 (9.8)	1023	169 (20.1)	840	157 (24.1)	651	148 (30.3)	488	611 (15.7)	3899
II	12 (3.4)	349	34 (9.7)	350	40 (15.8)	253	30 (22.1)	136	21 (40.4)	52	137 (12.0)	1140
III	7 (4.0)	174	22 (9.7)	226	45 (26.5)	170	32 (41.0)	78	19 (50.0)	38	125 (18.2)	686
IV	-	4	-	1	-	1	-	1	-	-	-	7
Total exposed	56 (3.9)	1424	156 (9.8)	1600	254 (20.1)	1264	219 (25.3)	866	188 (32.5)	578	873 (15.2)*	5732
Controls	3 (0.5)	664	15 (3.8)	400	36 (11.8)	305	17 (20.7)	82	9 (29.0)	31	80 (5.4)	1482

CO = No. of cases with corneal opacity
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, $p<0.01$ (Z test)

Corneal involvement. Tables 12.5 and 12.6 show that the prevalence rates of corneal involvement including corneal opacities (Figs. 12.6 to 12.8) were nearly three times more in the exposed population when compared with the control population ($p<0.01$), as also in each age group. As described earlier, corneal ulcers were seen in the exposed population in the acute phase, mostly in the inter-palpebral region. Band shaped keratitis (Fig. 12.6) was considered an important indicator of toxic gas exposure. Corneal oedema was also found to be more common in the exposed population.

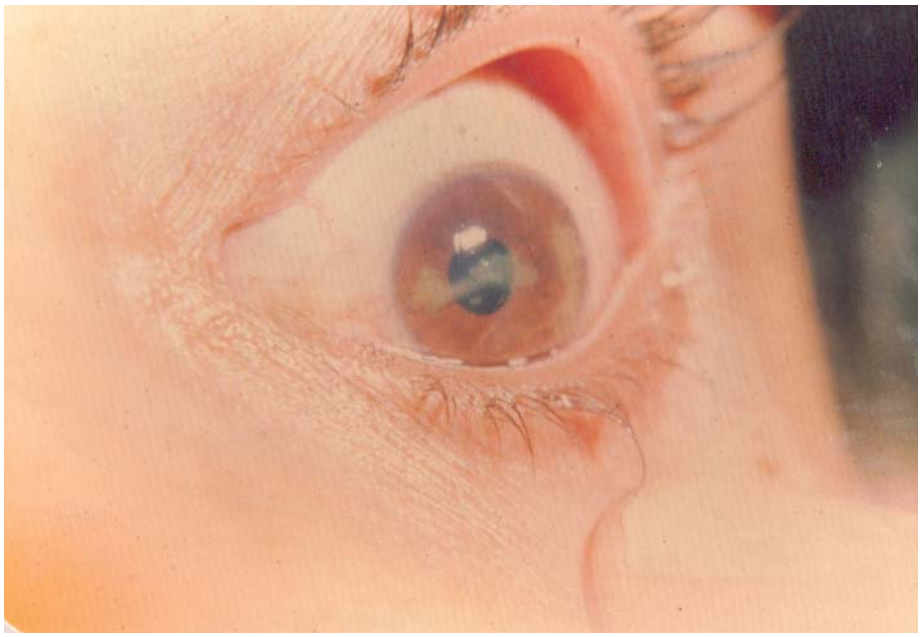

Fig. 12.6 Band shaped keratitis – a characteristic feature of exposure to toxic gas

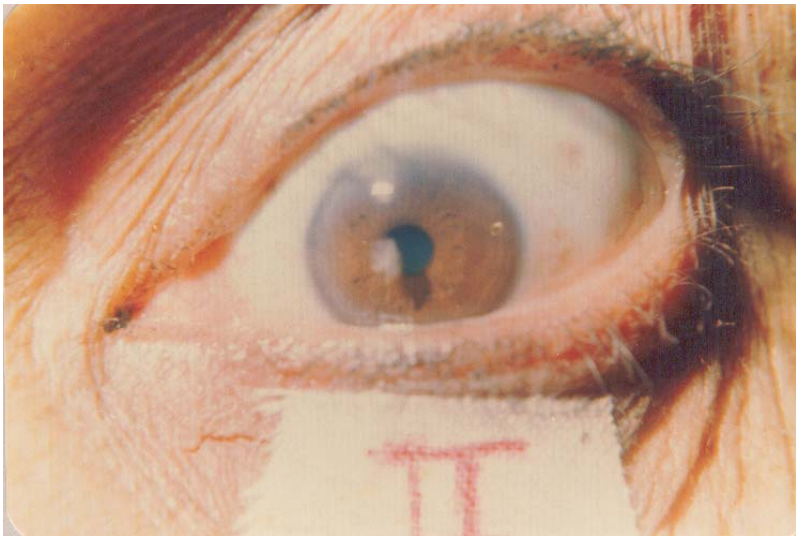

Fig. 12.7 Leucomatous corneal opacity

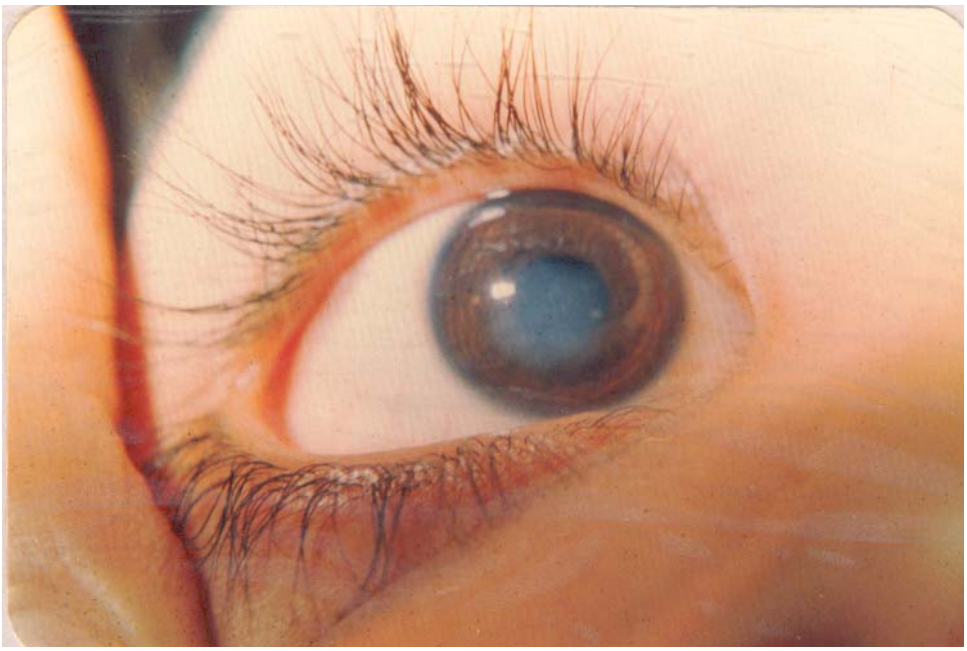

Fig. 12.8 Macular corneal opacity – opposite the pupil

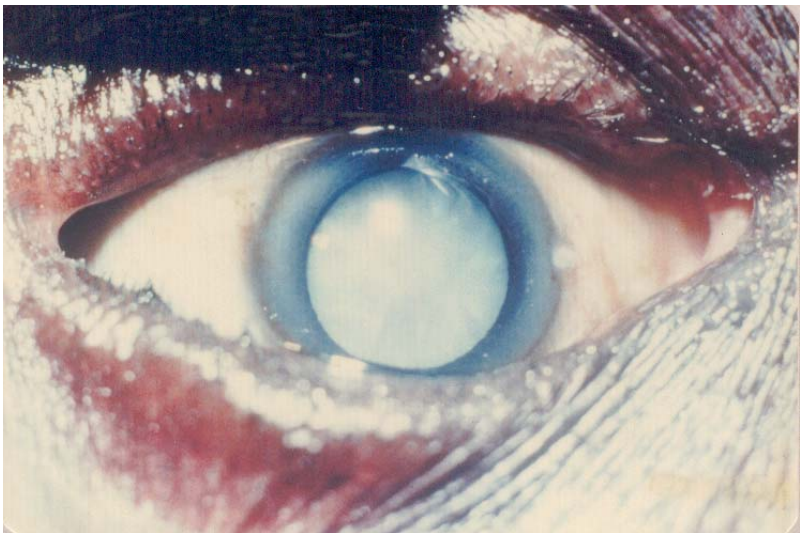

Fig. 12.9 Cataract

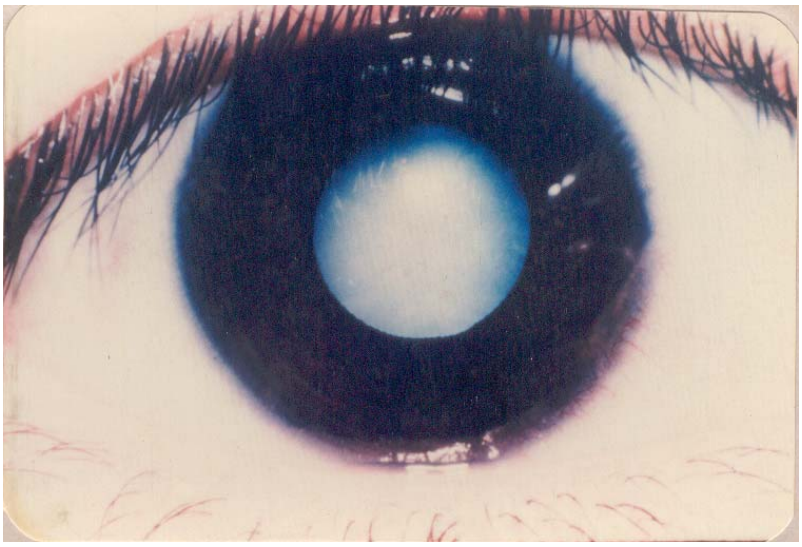

Fig. 12.10 Cataract

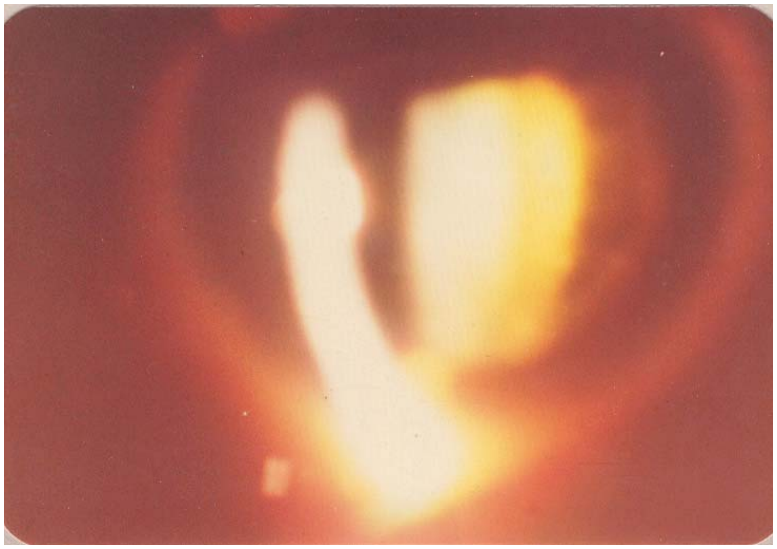

Fig. 12.11 Polychromatic lustre as seen with slit lamp

Lenticular opacities. The lenticular opacity data are presented in Table 12.7 and Figs. 12.9 to 12.11. It can be seen that the prevalence rates were significantly higher in the exposed group (8.7%) as compared with the control group (2.6%) with p value of <0.01. In both groups the prevalence rates increased with age. In the exposed group a higher proportion of persons in 45 to 59 years age group had developed cataract. There was also an indication of early onset of cataract in the exposees. In some of them the cataract was also found to have polychromatic lustre (Fig. 12.11), suggestive of its being of a complicated nature. The incidence of cortical type of cataract was found to be higher than of nuclear type.

Table 12.7 Lenticular Opacities in Various Age Groups of Exposed and Control Population

Age groups	0-14		15-29		30-44		45-59		>60		Total	
Exposed strata	LO	P	LO	P	LO	P	LO	P	LO	P	LO	P
I	8 (0.9)	897	3 (0.3)	1023	29 (3.5)	840	107 (16.4)	651	242 (49.6)	488	389 (10.0)	3899
II	2 (0.6)	349	5 (1.4)	350	14 (5.5)	253	17 (12.5)	136	27 (51.9)	52	65 (5.7)	1140
III	-	174	3 (1.3)	226	6 (3.5)	170	13 (16.7)	78	20 (52.6)	38	42 (6.1)	686
IV	-	4	-	1	-	1	-	1	-	-	-	7
Total exposed	10 (0.7)	1424	11 (0.7)	1600	49 (3.9)	1264	137 (15.8)	866	289 (50.0)	578	496 (8.7)*	5732
Controls	3 (0.5)	664	2 (0.5)	400	9 (3.0)	305	10 (12.2)	82	15 (48.4)	31	39 (2.6)	1482

LO = No. of cases with lenticular opacity
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, p<0.01 (Z test)

Fundus pathology. Table 12.8 shows that the prevalence rates of fundus abnormalities were significantly higher in the exposed (6.7%) as compared to the control (3.0%) population (p=<0.01). Age related - especially above 60 years - trends were also seen.

Table 12.8 Fundus Abnormality in Various Age Groups of Exposed and Control Population

Age groups	0-14		15-29		30-44		45-59		>60		Total	
Exposed strata	FA	P	FA	P	FA	P	FA	P	FA	P	FA	P
I	9 (1.0)	897	13 (1.3)	1023	46 (5.5)	840	91 (14.0)	651	147 (30.1)	488	306 (7.9)	3899
II	1 (0.3)	349	8 (2.3)	350	8 (3.2)	253	10 (7.4)	136	13 (25.0)	52	40 (3.5)	1140
III	1 (0.6)	174	1 (0.4)	226	14 (8.2)	170	10 (12.8)	78	13 (34.2)	38	39 (5.7)	686
IV	-	4	-	1	-	1	-	1	-	-	-	7
Total exposed	11 (0.8)	1424	22 (1.4)	1600	68 (5.4)	1264	111 (12.8)	866	173 (29.9)	578	385 (6.7)*	5732
Controls	5 (0.8)	664	6 (1.5)	400	13 (4.3)	305	12 (14.6)	82	9 (29.0)	31	45 (3.0)	1482

FA = No. of cases with fundus abnormality
P = Total no. of persons examined
Figures in parenthesis indicate percentage
*Significantly higher than control, p<0.01 (Z test)

Corneal Endothelium Studies

Ninety cases from the exposed area were subjected to specular microscopy for detailed examination of the corneal endothelium. The results of 75 cases could be obtained while in 15 cases due to the presence of gross corneal changes or due to other reasons (unco-operative patient, improper exposure etc.) reliable results could not be obtained. Thirty normal

individuals with no gross ocular pathology from unexposed area were also subjected to the endothelial studies (Table 12.9) to serve as control.

Table 12.9 Corneal Endothelium Mean Cell Density in Relation to Age Groups in Affected and Control Population

Age groups in years	No. of cases		Mean cell density	
	Affected	Control	Affected	Control
11-20	04	02	2322.0	2618.7
21-30	07	03	2238.2	2320.0
31-40	24	09	2224.2	2250.0
41-50	20	07	2157.0	2294.0
51-60	14	06	1929.0	2205.0
61-70	06	01	1675.0	1645.0
71-80	00	02	-	1487.0
Total	75	30	2090.95	2117.1

The mean cell density in the exposed population was observed to be less as compared to that in the unexposed/control population. In both groups the highest mean cell density was found in 11-20 year age group, and the lowest in the 71-80 year age group. Thirty-six cases out of 75 from the exposed population, with corneal opacities, showed mean cell densities as in Table 12.10.

Table 12.10 Corneal Endothelium Mean Cell Density in Corneal Opacity Cases

Age group in years	No. of cases with corneal opacity	Mean cell density
11-20	2	2350.0
21-30	6	2335.4
31-40	12	2195.8
41-50	7	2046.4
51-60	6	1860.8
61-70	3	1433.3
Total	36	2036

It was observed that mean cell density in these cases was low as compared with that in the rest of the cases from exposed group as well as the control group.

Table12.11Corneal Endothelium Quantitative Cell Analysis in Affected and Control Population

Age group in years	Polymegathism				Guttatta				Pigments			
	Affected No. of cases	%	Control No. of cases	%	Affected No. of cases	%	Control No. of cases	%	Affected No. of cases	%	Control No. of cases	%
11-20	1	25	-	-	-	-	-	-	-	-	-	-
21-30	-	-	-	-	-	-	-	-	-	-	-	-
31-40	1	4.16	-	-	1	4.16	-	-	2	9	-	-
41-50	4	20	-	-	3	15	2	28.5	1	5	-	-
51-60	11	78.5	4	66.6	7	50	3	50	-	-	-	-
61-70	4	66.6	1	100	3	50	1	100	1	16.6	-	-
71-80	-	-	1	50	-	-	2	100	-	-	-	-
Total	21	28	6	20	14	18.6	8	26.6	4	5.3	-	-

Out of 75 cases from exposed population, polymegathism was found in 21 (28%) cases as compared to 6 (20%) out of 30 cases in the control population. While guttatta was observed in 14 cases (18.66%) in the exposed population, it was so in only 8 cases (26.6%) in the

control population. Pigments were seen in 4 cases (5.3%) in the exposed group (Table 12.11).

Table 12.12 orneal Endothelium Quantitative Cell Analysis in Corneal Opacity Cases

Age group in years	Polymegathism		Guttatta		Pigments	
	No. of cases	%	No. of cases	%	No. of cases	%
11-20	-	-	-	-	-	-
21-30	-	-	-	-	-	-
31-40	1	8.33	1	8.33	2	16.66
41-50	2	28.57	2	28.57	1	14.28
51-60	5	83.33	4	66.66	-	-
61-70	3	100	2	66.66	-	-
Total	11	30.55	9	25	3	8.33

Out of 36 cases showing corneal opacities in the exposed group, 11 cases (30.55%) had polymegathism, 9 cases (25%) showed guttatta and 3 cases (8.33%) had pigments. Thus, the corneal opacity cases showed a higher incidence of polymegathism and guttatta changes as compared to other groups (Table 12.12). A long-term follow up of the cases showing corneal opacities would be required to detect any further changes in the corneal endothelium.

PHASE II STUDY (September 1988 to September 1992)

OBJECTIVES

The broad aims of Phase II study were to reassess the prevalence of ocular diseases in the gas affected areas after an interval of 3-4 years. This had two parts : (i) a second prevalence study, and (ii) in-depth study.

MATERIAL AND METHODS

A sample of 4946 persons was selected from one locality each from areas designated as severely, moderately, mildly exposed and control/unexposed (Table 12.13). This was called the Second Prevalence Survey. The data were compared with the Phase I study data. The methodology used was the same in both studies.

Table 12.13 Distribution of Sample Provided and Studied in Second Prevalence Survey : Phase II Study

Exposure	Locality number	Sample provided	Number studied
Severe	02	2012 (29.1)	1377 (47.3)
Moderate	04	2207 (22.0)	1288 (58.4)
Mild	11	2657 (26.5)	1227 (46.2)
Control	15	2238 (22.4)	1054 (47.3)
Total		9114	4946 (49.4)

Figures in parenthesis indicate percentage

OBSERVATIONS AND DISCUSSION

The results of the second prevalence study are presented in Tables 12.14 to 12.25. For comparison of Phase II with Phase I, the prevalence data of 1st phase of the respective locality has been presented. It may be noted that in Phase I, exposed persons were stratified into four categories based on the symptoms related to gas exposure and their chronicity etc. In Phase II, the presentation was based on the severity of exposure, viz., severe, moderate or mild as categorized by the Municipal Corporation. Although the same population has been studied in the two Phases, the prevalence rates of Phase I data of all localities were slightly different.

Table 12.14 shows the prevalence rates of trachoma seen in various areas in different age groups. When compared to the controls, the proportion of cases in the total exposed group were significantly higher (20.4%) than the control group (12.0%), when all the age groups and areas were considered together ($p<0.01$). Within the exposed group no difference or gradation in the prevalence of trachoma in relation to degree of exposure was observed. However, with increase in age, the proportion of trachoma cases increased in both exposed and control groups.

Table 12.14 Prevalence Rates of Trachoma in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**T**	**P**	**T**	**P**	**T**	**P**	**T**	**P**	**T**	**P**	**T**	**P**
SEVERE Phase II	10 (1.5)	675	43 (12.5)	345	70 (33.0)	212	44 (48.4)	91	32 (59.3)	54	199 (14.5)	1377
Phase I	-	77	6 (6.4)	94	20 (18.7)	107	26 (36.1)	72	36 (45.6)	79	88 (20.5)	429
MODERATE Phase II	15 (5.4)	278	38 (10.8)	351	91 (33.2)	274	157 (57.7)	272	75 (67.0)	112	376 (29.2)	1287
Phase I	1 (1.3)	74	11 (11.3)	97	43 (38.0)	113	44 (49.4)	89	41 (72.0)	57	140 (32.6)	430
MILD Phase II	-	252 (2.9)	9	308 (24.0)	88	366 (33.2)	72	217 (57.1)	48	84 (17.0)	217	1277
Phase I	1 (2.6)	39	2 (4.8)	42	11 (23.0)	48	9 (32.1)	28	10 (45.4)	22	33 (18.4)	179
TOTAL EXPOSED Phase II	25 (2.1)	1205	90 (9.0)	1004	249 (29.2)	852	273 (47.1)	580	155 (62.0)	250	792 (20.4)	3891
Phase I	2 (1.0)	190	19 (8.1)	233	74 (27.6)	268	79 (41.8)	189	87 (55.0)	158	261 (25.1)	1038
CONTROL Phase II	13 (3.0)	435	18 (6.1)	296	51 (22.2)	230	28 (45.9)	61	16 (50.0)	32	126 (12.0)	1054
Phase I	35 (2.6)	189	18 (14.0)	129	31 (28.0)	111	11 (40.7)	27	6 (60.0)	10	71 (15.2)	466

T = No. of cases with active or healed trachoma
P = Total no. of persons surveyed
Figures in parenthesis indicate percentages

TIME TRENDS

The prevalence rates of trachoma showed a slight decrease in both the total exposed (25% Phase I vs 20% Phase II) as well as control groups (15% Phase I vs 12% Phase II). Thus, after about 2 years a decrease in trachoma prevalence was observed.

Table 12.15 shows the prevalence rates of chronic irritative conjunctivitis seen in various age groups of exposed (severe, moderate and mild) and control areas. When all the age groups and exposed areas were pooled together, the proportion of cases with chronic irritative conjunctivitis was significantly higher in exposed group (23.3%) than in the control group (15.3%) ($p<0.01$). Chronic conjunctivitis was more prevalent in severe areas than in moderately or mildly exposed areas. The manifestations of chronic irritative conjunctivitis

were a direct effect of gas exposure. In the respective age groups no consistent pattern or gradation could be seen in the exposed or control groups. In Phase I study (Table 12.3 and 12.4) a gradually increasing trend with increase in age was observed in the proportion of trachoma and chronic irritative conjunctivitis (congestion) for both exposed and control areas. However, in Phase II no such systematic gradation was observed as the trends appear to be fluctuating.

The proportion of chronic irritative conjunctivitis showed an appreciable decline in both the total exposed (47.2% in Phase I vs 23.3% in Phase II) as well as control groups (28% in Phase I vs 15.3% in Phase II). Over time, a decline in chronic conjunctivitis was observed.

Table 12.16 shows the proportion of cases with conjunctival xerosis. Its prevalence was observed to be significantly higher in the control group(8.3%) as compared to the total exposed group (2.3%) in Phase II. A similar trend was observed in Phase I also (2.6% in control vs 1.6% in exposed. It was observed that children below 14 years of age were predominantly affected in all the areas and in both Phases.

Table 12.15 Prevalence Rates of Chronic Irritative Conjunctivitis in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
SEVERE												
Phase II	123 (18.2)	675	113 (32.7)	345	77 (36.2)	212	36 (39.6)	91	16 (29.6)	54	365 (26.5)	1377
Phase I	15 (19.5)	77	31 (33.0)	94	63 (58.9)	107	47 (65.3)	72	60 (76.0)	79	216 (50.3)	429
MODERATE												
Phase II	38 (13.7)	278	97 (27.6)	351	74 (27.0)	275	70 (25.7)	272	33 (29.5)	112	312 (24.2)	1287
Phase I	15 (20.3)	74	32 (33.0)	97	39 (34.5)	113	23 (25.8)	89	14 (24.6)	57	123 (28.6)	430
MILD												
Phase II	29 (11.5)	252	50 (16.2)	308	87 (23.8)	366	52 (24.0)	217	11 (13.1)	84	229 (18.7)	1227
Phase I	12 (30.8)	39	10 (23.8)	42	16 (33.3)	48	14 (50.0)	28	12 (54.5)	22	64 (35.7)	179
TOTAL EXPOSED												
Phase II	190 (15.8)	1205	260 (25.9)	1004	238 (28.0)	852	158 (27.2)	580	60 (24.0)	250	906 (23.3)	3891
Phase I	42 (22.1)	190	73 (31.3)	233	118 (44.0)	268	84 (44.4)	189	86 (54.4)	158	403 (38.8)	1038
CONTROL												
Phase II	35 (8.0)	435	46 (15.5)	296	61 (26.5)	230	14 (21.0)	61	5 (15.6)	32	161 (15.3)	1054
Phase I	18 (9.5)	189	42 (32.5)	129	56 (50.4)	111	10 (37.0)	27	4 (40.0)	10	130 (28.0)	466

C = No. of cases with chronic irritative conjunctivitis
P = Total no. of persons examined
Figures in parenthesis indicate percentages

Table 12.16 Prevalence Rates of Conjunctival Xerosis in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
SEVERE Phase II	51 (7.5)	675	9 (2.6)	345	2 (0.9)	212	-	91	1 (1.8)	54	63 (4.6)	1377
Phase I	6 (7.8)	77	1 (1.0)	94	-	107	1 (1.4)	72	-	79	8 (1.9)	429
MODERATE Phase II	11 (4.0)	278	3 (0.8)	351	6 (2.2)	274	3 (1.1)	272	-	112	23 (1.8)	1287
Phase I	1 (1.3)	74	-	97	2 (1.8)	113	2 (2.2)	89	-	57	5 (1.2)	430
MILD Phase II	1 (0.4)	252	2 (0.6)	308	2 (0.5)	366	-	217	-	84	5 (0.4)	1227
Phase I	1 (2.6)	39	-	42	-	48	-	2	-	22	1 (0.5)	179
TOTAL EXPOSED Phase II	63 (5.2)	1205	14 (1.4)	1004	10 (1.2)	852	3 (0.5)	580	1 (0.4)	250	91 (2.3)	3891
Phase I	8 (4.2)	190	1 (0.4)	233	2 (0.7)	268	3 (1.6)	119	-	158	14 (1.3)	1038
CONTROL Phase II	50 (11.5)	435	29 (9.8)	296	7 (3.0)	230	1 (1.6)	61	1 (3.1)	32	88 (8.3)	1054
Phase I	6 (3.2)	189	5 (3.9)	129	1 (0.9)	111	-	27	1 (10.0)	10	12 (2.6)	466

C = No. of cases with conjunctival xerosis
P = Total no. of persons examined
Figures in parenthesis indicate percentages

In Phase II the prevalence of conjunctival xerosis showed an increase in both the total exposed (1.3% in Phase I vs 2.3% in Phase II) as well as control (2.6% in Phase I vs 8.3% in Phase II). This may be due to a decline in the health care facilities, lack of vitamin A supplement etc. in the control areas.

Table 12.17 shows the prevalence rates of corneal involvement in various age groups of exposed and control areas. It was observed that the prevalence of corneal involvement was higher (20.6%) in the exposed group than in the control group (8.5%). In each age group as well, the exposed group had more corneal abnormalities than the controls. Similar trends were seen in Phase I also (Table 12.6). The prevalence of corneal involvement was greater in Phase II in both the exposed (16.5% in Phase I vs 20.6% in Phase II) and control groups (5.1% in Phase I vs 8.5% in Phase II). This suggests continuing corneal involvement with deterioration after the exposure. “Corneal opacities” were detected by slit lamp examination carried out at the CCU (hospital and field). Further corneal decompensation was observed by specular microscopy in these cases to exclude any qualitative and quantitative change in corneal endothelium.

The prevalence rates of corneal opacities are presented in Table 12.18. It can be seen that in the total exposed group a significantly higher proportion of persons had corneal opacities (16.6%) as compared to the non-exposed controls (8.5%) in Phase II ($p<0.01$). Over time, in the exposed group the prevalence rates remained almost the same (Phase II 16.6% vs Phase I 15.3%). On the other hand, an increase was observed in the controls (5.0% in phase I vs 8.5% in Phase II). A gradually increasing prevalence rates of "corneal opacities" with increase in age groups was observed in Phase II in both exposed and control areas, thereby suggesting that older age groups had greater exposure to toxic gas whereas the children may have been carried or protected while they were running away at the time of gas leak. The mildly exposed areas had lower prevalence (8.9%) as compared to the severely (17.4%) and moderately (23.0%) exposed areas. In Phase I, the severe area had higher prevalence (20.0%) as compared to moderate (10.5%) or mild (15.6%) areas.

Table 12.17 Prevalence Rates of Corneal Involvement in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
SEVERE												
Phase II	51 (7.5)	675	63 (18.3)	345	62 (29.2)	212	31 (34.0)	91	26 (48.1)	54	233 (17.0)	1377
Phase I	7 (9.1)	77	7 (7.4)	94	23 (21.5)	107	16 (22.2)	72	35 (44.3)	79	88 (20.5)	429
MODERATE												
Phase II	26 (9.3)	278	47 (13.4)	351	72 (26.3)	274	100 (36.8)	272	54 (48.2)	112	299 (23.2)	1287
Phase I	2 (2.7)	74	1 (1.0)	97	13 (11.5)	113	15 (16.8)	87	10 (17.5)	57	41 (9.5)	430
MILD												
Phase II	96 (38.1)	252	59 (19.1)	308	56 (15.3)	366	42 (19.3)	217	16 (19.0)	84	269 (22.0)	1227
Phase I	1 (2.5)	39	8 (19.0)	42	17 (35.4)	48	7 (25.0)	28	9 (41.0)	22	42 (23.5)	179
TOTAL EXPOSED												
Phase II	173 (14.3)	1205	169 (16.8)	1004	190 (22.3)	852	173 (29.8)	580	96 (38.4)	250	801 (20.6)	3891
Phase I	10 (5.3)	190	16 (6.9)	233	53 (19.8)	268	38 (20.1)	189	54 (34.2)	158	171 (16.5)	1038
CONTROL												
Phase II	11 (2.5)	435	14 (4.7)	296	45 (19.6)	230	11 (18.0)	61	9 (28.1)	32	90 (8.5)	1054
Phase I	1 (0.5)	189	5 (3.9)	129	14 (12.6)	111	2 (7.4)	27	2 (20.0)	10	24 (5.1)	466

C = No. of cases with corneal involvement
P = Total no. of persons examined
Figures in parenthesis indicate percentages

Table 12.18 Prevalence Rates of Corneal Opacity in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
SEVERE												
Phase II	51 (7.5)	675	66 (19.1)	345	63 (29.7)	212	32 (35.2)	91	28 (51.8)	54	240 (17.4)	1377
Phase I	7 (9.1)	77	7 (7.4)	94	22 (20.6)	107	16 (22.2)	72	34 (43.0)	79	86 (20.0)	429
MODERATE												
Phase II	27 (9.7)	278	47 (13.4)	351	70 (25.5)	274	100 (36.8)	272	52 (46.4)	112	296 (23.0)	1287
Phase I	2 (2.7)	74	1 (1.0)	97	14 (12.4)	113	16 (18.0)	89	12 (21.0)	57	45 (10.5)	430
MILD												
Phase II	4 (1.6)	252	15 (4.9)	308	40 (11.0)	366	33 (15.2)	217	17 (20.2)	84	109 (8.9)	1227
Phase I	2 (5.1)	39	3 (7.1)	42	10 (20.8)	48	5 (17.8)	28	8 (36.4)	22	28 (15.6)	179
TOTAL EXPOSED												
Phase II	82 (6.8)	1205	128 (12.7)	1004	173 (20.3)	852	165 (28.4)	580	97 (38.8)	250	645 (16.6)	3891
Phase I	11 (5.8)	190	11 (4.7)	233	46 (17.2)	268	37 (19.6)	189	54 (34.2)	158	159 (15.3)	1038
CONTROL												
Phase II	11 (2.5)	435	14 (4.7)	296	45 (19.6)	230	11 (18.0)	61	9 (28.1)	32	90 (8.5)	1054
Phase I	1 (0.5)	189	5 (3.9)	129	13 (11.7)	111	2 (7.4)	27	2 (20.0)	10	23 (5.0)	466

C = No. of cases with corneal opacity
P = Total no. of persons examined
Figures in parenthesis indicate percentages

The prevalence rates of "lenticular opacities" are presented in Table 12.19. It can be seen that in Phase II the prevalence rates of cataract was significantly higher in the total exposed group (11.0%) as compared to the controls (4.2%) ($p<0.01$). Similar trends were seen in Phase I also (Table 12.17 and 12.9). In the age group of <14 years, 15-29 and 30-44 years, no significant differences in the prevalence rates of cataract were observed in the exposed and control groups in Phase II. However, in 45-59 years age group a significantly higher prevalence was observed in the exposed group (33.6%) as compared to the control group (19.7%). This suggests early onset of cataract in the exposed population. In the severe area, the prevalence of cataract was found to be lower than moderate and mild areas in Phase II, whereas in Phase I, severe area had higher prevalence. Such differences in prevalence rates reflect better surgical treatment facilities in the severe area.

TIME TRENDS

In the exposed group, a slight decrease in the prevalence rates of cataract was recorded in Phase II (11.0%) as compared to Phase I (13.3%), whereas in the control group it remained almost similar.

Table 12.19 Prevalence Rates of Lenticular Opacities in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
SEVERE												
Phase II	4 (0.6)	675	7 (2.0)	345	12 (5.7)	212	28 (30.8)	91	31 (57.4)	54	82 (6.0)	1377
Phase I	-	77	1 (1.0)	94	2 (1.9)	107	15 (20.8)	72	42 (53.2)	79	60 (14.0)	429
MODERATE												
Phase II	1 (0.3)	278	6 (1.7)	351	21 (7.7)	274	92 (33.8)	272	88 (78.6)	112	208 (16.2)	1287
Phase I	1 (1.3)	74	1 (1.0)	97	5 (4.4)	113	18 (20.2)	89	30 (52.6)	57	55 (12.8)	430
MILD												
Phase II	2 (0.8)	252	1 (0.3)	308	17 (4.6)	366	63 (29.0)	217	57 (67.8)	84	140 (11.4)	1227
Phase I	-	39	1 (2.4)	42	1 (2.1)	48	7 (25.0)	28	14 (63.6)	22	23 (12.8)	179
TOTAL EXPOSED												
Phase II	7 (0.6)	1205	14 (1.4)	1004	50 (5.9)	852	195 (33.6)	580	176 (70.4)	250	430 (11.0)	3891
Phase I	1 (0.5)	190	3 (1.3)	233	8 (3.0)	268	40 (21.2)	189	86 (54.4)	158	138 (13.3)	1038
CONTROL												
Phase II	4 (0.9)	435	4 (1.3)	296	9 (4.0)	230	12 (19.7)	61	15 (46.9)	32	44 (4.2)	1054
Phase I	3 (1.6)	189	4 (3.1)	129	2 (1.8)	111	4 (14.8)	27	6 (60.0)	10	19 (4.0)	466

C = No. of cases with lenticular opacity
P = Total no. of persons examined
Figures in parenthesis indicate percentages

The prevalence rates of fundus abnormality are presented in Table 12.20. It can be seen that the total exposed group had higher abnormality (6.22%) as compared to control (4.3%) in Phase II as well as in Phase I (7.3% and 2.4% respectively). With increase in age, the abnormality prevalence increased in all areas. Fundus pathology was mainly in the form of pigmentary changes at the macular region.

TIME TRENDS

In the exposed areas the prevalence of fundus abnormality decreased in Phase II whereas in control areas it increased. This, however is believed to be not related to gas exposure.

The data presented thus show that the exposure to toxic gas resulted in conjunctival, corneal and lenticular involvement in the acute stage which later resulted in irreversible changes as evidenced by chronic irritative conjunctivitis, corneal opacities, lenticular opacities with polychromatic lustre and early onset of cataract.

Table 12.20 Prevalence Rates of Fundus Pathology in Various Age Groups of Severely, Moderately, Mildly Exposed and Control Areas : Phase II and Phase I

Age groups	<14		15-29		30-44		45-59		>60		Total	
AREAS	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	C	P
SEVERE Phase II	3 (0.4)	675	7 (2.0)	345	11 (5.2)	212	11 (12.1)	91	22 (40.7)	54	54 (4.0)	1377
Phase I	-	77	1 (1.0)	94	3 (2.8)	107	5 (7.0)	72	17 (21.5)	79	26 (6.1)	429
MODERATE Phase II	-	278	6 (1.7)	351	19 (7.0)	274	47 (17.3)	272	51 (45.5)	112	123 (9.5)	1287
Phase I	1 (1.3)	74	1 (1.0)	97	5 (4.4)	113	9 (10.1)	89	18 (31.6)	57	34 (8.0)	430
MILD Phase II	-	252	2 (0.6)	308	24 (6.5)	366	16 (7.4)	217	23 (27.4)	84	65 (5.3)	1227
Phase I	-	39	1 (2.4)	42	1 (2.1)	48	3 (10.7)	28	11 (50.0)	22	16 (9.0)	179
TOTAL EXPOSED Phase II	3 (0.2)	1205	15 (1.5)	1004	54 (6.3)	852	74 (12.7)	580	96 (38.4)	250	242 (6.2)	3891
Phase I	1 (0.5)	190	3 (1.3)	233	9 (3.3)	268	17 (9.0)	189	46 (29.1)	158	76 (7.3)	1038
CONTROL Phase II	6 (1.4)	435	5 (1.7)	296	13 (5.6)	230	8 (13.1)	61	13 (40.6)	32	45 (4.3)	1054
Phase I	2 (1.0)	189	1 (0.7)	129	2 (1.8)	111	3 (11.1)	27	3 (30.0)	10	11 (2.4)	466

C = No. of cases with fundus pathology
P = Total no. of persons examined
Figures in parenthesis indicate percentages

IN-DEPTH STUDY - PHASE II

The in-depth study of Phase II was aimed at a repeat of detailed ocular examination of all the persons detected to have ocular abnormalities in Phase I compared with 20% of normals. A total of 864 persons i.e., 1728 eyes were examined in detail in the two Phases with a gap of about 2 years. The data have been presented for Phase I and Phase II in Table 12.21, wherein horizontal columns pertain to Phase I while vertical figures pertain to Phase II. It is therefore possible to understand any progression in disease pattern over time.

Table 12.21 Distribution of Various Grades of Trachoma in 1,728 Eyes Examined in Phase I and Phase II

Phase I (horizontal columns)	**Phase II (vertical columns)**					
	Normal	**1**	**2**	**3**	**4**	Total
Normal	961	4	35	111	63	1174
1	-	-	-	-	-	-
2	68	-	10	48	12	138
3	122	-	18	130	68	338
4	18	-	4	34	22	78
Total	1169	4	67	323	165	1728

1 – grade 1 trachoma; 2 – grade 2 trachoma; 3 – grade 3 trachoma; 4 – grade 4 trachoma

Table 12.21 shows the distribution of various grades of trachoma in Phase I and Phase II. Trachoma was classified as Grade 1 (active trachoma) includes incipient trachoma, Grade 2 (established lesions), Grade 3 (healing lesions) and Grade 4 (healed lesions). In Phase I, 1174 eyes were normal whereas in Phase II, 1169 eyes were normal. There was a marginal decrease in the number of normals in Phase II. Within the abnormal group, 78 eyes showed healed lesions in Phase I whereas in Phase II 165 eyes showed healed lesions. Thus, a shift in the distribution from active/healing lesions to healed lesions was observed. This is suggestive of beneficial results of therapy as well as time related healing.

Table 12.22 Distribution of Chronic Irritative Conjunctivitis in Phase I and Phase II

Phase I (horizontal columns)	**Phase II (vertical columns)**			
	Normal	**Abnormal**	**Total**
Normal	655	173	828
Abnormal	583	316	899
Total	1238	489	1727

Table 12.22 shows the distribution of chronic irritative conjunctivitis in Phases I and II. A marked increase in number of eyes with no conjunctivitis was recorded in Phase II as compared to Phase I (1238 vs 828). This means that the earlier marked reaction to the toxic gas in Phase I diminished later on in Phase II. Eight hundred and ninety nine eyes however continued to have irritative conjunctivitis.

Table 12.23 Corneal Involvement in Phase I and Phase II

Phase I (horizontal columns)	**Phase II (vertical columns)**		
	Normal	Abnormal	Total
Normal	977	197	1174
Abnormal	83	471	554
Total	1060	668	1728

The number of eyes in which any corneal abnormality was detected was observed to be 554 (32.1%) in Phase I whereas in Phase II this number was 668 (38.7%) (Table 12.23). A deterioration in corneal involvement was observed in Phase II as compared to Phase I. This was despite the inputs in terms of treatment etc.

Table 12.24 Distribution of Types of Corneal Opacities in Phase I and Phase II

Phase I (horizontal columns)		**Phase II (vertical columns)**				
		Normal	Nebular	Macular	Leucoma	Total
	Normal	981	108	1	100	1190
	Nebular	43	92	1	73	209
	Macular	3	7	-	19	29
	Leucoma	-	63	41	196	300
	Total	1027	270	43	388	1728

Table 12.25 Distribution of Lenticular Opacity in 1,728 Eyes Examined in Phases I & II

Phase I (horizontal columns)		Phase II (vertical columns)		
		Normal	Cataract	Total
	Normal	1166	133	1299
	Cataract	21	408	429
	Total	1187	541	1728

Corneal opacities were examined by a slit lamp at the comprehensive care unit (CCU). Table 12.24 shows the distribution of type of corneal opacities in the two phases and graded nebular (codes 1 & 2), macular (codes 3 & 4) and leucomatous (codes 5, 6, 7, 8 & 9) on the basis of the extent of the opacity. The number of normals were found to be greater in Phase I (1190) as compared to Phase II (1027). All the three types of opacities were found to be greater in

Phase II, nebular (209), macular (29) and leucomatous (300) groups respectively as compared to Phase I, in the nebular (270), macular (43) and leucomatous (283) groups respectively. These results indicate that there was a deterioration over time in the extent/ type of corneal opacities.

Table 12.25 shows the distribution of lenticular opacities in Phase I and Phase II. An increase in the number of cataracts was observed over time (561 in Phase II vs 428 in Phase I). The type of cataract was classified as senile or others. It was observed that in Phase I, 348, i.e. 81.3% of the cataracts were of senile variety. In Phase II, 351 cataracts, i.e., 62.6% were observed to be senile variety. This indicates that 19% and 37% of cataracts were of complicated type in Phase I and Phase II respectively. Polychromatic lustre was observed in some of these by slit lamp examination.

CONCLUSIONS

1. The prevalence rate studies in Phase I and Phase II show that the prevalence of trachoma was significantly higher in the exposed areas as compared to the control and no change after 3-4 yeas was observed in Phase II as compared to Phase I.
2. The prevalence rates of chronic irritative conjunctivitis was also observed to be higher in the exposed areas as compared to the unexposed/control areas. After 3-4 years, although the prevalence rates decreased in both areas, it remained significantly higher in the exposed areas as compared to the control areas. Chronic irrirative conjunctivitis had developed due to exposure to the toxic gas.
3. Conjunctival xerosis, a feature of hypo-vitaminosis was reported to be higher in control areas as compared to the exposed areas. When the prevalence was re-estimated after 3-4 years, an increase in prevalence of conjuctival xerosis was observed in both the areas.
4. Prevalence rates of corneal opacities was seen to be significantly higher in the exposed population as compared to the unexposed/control population. The lesions were seen in the interpalpebral region in some cases. These band shaped opacities occurred due to gas hitting the partially closed eyes. Over time, a slight increase in corneal opacities was observed in exposed as well as control areas. This may be due to improved diagnostic facilities.
5. The prevalence rates of cataract was seen to be higher in the exposed group as compared to the control group in both Phase I and Phase II studies. Polychromatic lustre was observed in some cases, indicating that cataract was of “complicated type”. In the exposed persons, it was also seen to occur at an earlier age as compared to the unexposed/controls.
6. Fundus abnormalities mainly in the form of pigmentary changes at the macular area were observed. They were significantly higher in exposed areas as compared to control areas. No specific change over time was observed.
7. These results indicate that toxic gas exposure resulted in ocular morbidity which in some cases was progressive. There is a need to follow up these persons to assess the extent of damage and disease progression.

Chapter 13

Study of Oral Mucosal Gingival and Oro-dental Anomalies in Children whose Mothers were Exposed to MIC/Toxic Gas during Pregnancy

(Study Period : November 1986 to June 1991)

OBJECTIVES

To study the following in children born to mothers who were exposed to MIC/toxic gas during pregnancy in December 1984:

- Oro-dental, mucosal and gingival anomalies
- Eruption trends of deciduous dentition
- Changes in arch width and palatal height and development in occlusion.

MATERIAL AND METHODS

Initially, 1216 children from the affected and 663 children from the unaffected/control areas were included in the study. Later, as per advice of PAC in April 1987, 801 children were taken from Area Code No.14, 15, 16 and 25 out of about 3000 cases of the locality.

A comprehensive proforma with a "Work Manual" was prepared to record oro-dental malformations, tooth eruption, dental occlusion, oral mucosal changes including tongue and gingivae, facial heights, facial width and lastly the dental arch and palatal height measurements. The "Field Staff" was duly trained for examination and recording of measurements according to the "Work Manual". Till 31st March 1990, 8 visits of affected and control groups had been completed by a door-to-door clinical examination at 4 monthly intervals till the 5th visit, and at six monthly interval thereafter. The data of these 8 visits and even that of 9th visit were submitted to Computer Centre for anlaysis.

In addition to clinical examination, since December 1988 upper and lower impressions of randomly selected children of both affected and control group (200 each) were taken and plaster casts prepared to study dental arch dimensions and palatal height, repeated at yearly interval. Till November 1990, two sets of measurements were recorded and analysed manually.

OBSERVATIONS

Some of the observations based on clinical examination and manual analysis are given below:

1. No congenital malformation of face and arches could be seen in the affected group compared with control group.
2. No significant changes could be observed in oral mucosa, gingivae and tongue as regards colour, texture, pigmentation, keratinization patches etc. in both the affected and control groups.

However, 56 children of affected group showed ulcers on tongue (132), palate (10), labial mucosa (4), buccal mucosa (6), floor of the mouth (2), angle of mouth (2), and only 3

children from unaffected area had ulcers on tongue. These ulcers disappeared spontaneously by the 6th visit. In addition, in affected group, cases of tongue tie (8) benign migratory glossitis (3) and tiny growth on tongue (1) were also noted.

3 No numerological morphological, visual, histological anomaly or discoloration were noted in both groups except fusion of deciduous incisors (5) and neonatal teeth in one.

4 Eruption trends in both the groups showed a slightly disturbed and delayed pattern – more in control group. However, both catch normal standards (available western data) by completion of eruption of all deciduous dentition.

5 Facial heights and bizygomatic width showed very slight difference in affected and control groups. Affected group seemed to be slightly behind compared with the control group.

6 One time dental arch dimensions i.e. intermolar, intercanine width and palatal heights the two groups also did not show any significant difference. However, to draw any final conclusions, these cases must be followed up to the age of 7 yeas, as the active arch changes take place between age of 4 to 7 years.

Chapter 14

Cancer Patterns in MIC Affected and Un-Affected Areas of Bhopal (1988-2003)

INTRODUCTION

NATIONAL CANCER REGISTRY PROGRAMME

The Indian Council of Medical Research initiated a network of Cancer Registries across the country under the National Cancer Registry Programme (NCRP) in December 1981. This move followed the recognition that there was an urgent need for strengthening the existing cancer registries and organization of new cancer registries in different regions of the country. The programme was commenced with the objectives of generating reliable data on the magnitude and patterns of cancer, to undertake epidemiologic studies in the form of case control or cohort studies based on observations of registry data; provide research base for developing appropriate strategies to aid in National Cancer Control Programme; and, develop human resource in cancer registration and epidemiology. As of 2008 there are 20 Population - and 5 Hospital Based Cancer Registries under the NCRP network. The NCRP is a long-term activity of the Indian Council of Medical Research. The programme is one of the many major activities of the Division of Non-Communicable Diseases. The Programme is assisted by a Steering Committee that meets periodically to oversee and guide its functioning. A review meeting is held annually where the Principal Investigators and staff of the Registries, under the NCRP, present data and participate in the discussions. The entire activities of the NCRP are coordinated by the Centre located in Bangalore.

Following the accident that led to the leakage of Methyl-Isocyanate (MIC) and its related toxic gas products, the Indian Council of Medical Research set up a Population Based Cancer Registry at Bhopal with the following objectives:

1. Registration of all cancer cases of residents of Bhopal and generate a data base.
2. To observe and compare the incidence rates of cancer (all sites) in MIC/toxic gas affected and un-affected areas of Bhopal.
3. To assess the time trend in the incidence of various types of cancer in the two areas.

* National Cancer Registry Programme (NCRP) - ICMR

The registry that was commenced under the National Cancer Registry Programme (NCRP) of the ICMR started collecting data from 1st January 1988.

Soon after the industrial accident, the Bhopal Municipal area was divided into gas affected and un-affected areas. The demarcation of the areas was based on the number of deaths in these areas between 3rd and 6thDecember 1984. Thus, the 56 Municipal Wards of Bhopal, were categorized, into 36 wards that were considered as ‘gas affected’ and 20 Wards that were considered as ‘gas un-affected’.

The following brief write-up gives an idea of the cancer patterns and trends in the various anatomical sites of cancer in the two areas. It also highlights trends over time in the incidence rates of cancer.

METHODS AND MATERIALS

Cancer Registration is the process of systematically and continuously collecting information on malignant neoplasms. Broadly there are two types of Cancer Registries - Hospital based (HBCR) and Population based (PBCR).

Hospital based cancer registries collect information of cancers reported in a given hospital, regardless of where that person with cancer resides. Hospital based registries help in assessing cancer patient care in a given hospital and aid in hospital administration including the individual hospital's cancer control programmes.

Population based cancer registries collect information of all new cancer cases reported from the population residing in a defined geographic area. PBCRs are concerned with providing information on cancer incidence and mortality, trends over time and constitute a base for carrying out research studies on cancer etiology through epidemiologic studies. There are several sources from where staff of registries, collect information on cancer cases. These include pathology reports, medical records, radiology and radiotherapy departments and death certificates to name a few. The methodology of data collection by the registries in India is active in that registry staff, regularly and periodically visit various sources to actively pursue and collect information in a standard 'core form' on cancers reported and interview patients wherever possible. The advent of computing technology and the age of electronic information processing have transformed working of registries in India as elsewhere in the world.

Details of the methods of working of the population based cancer registry, standard guiding principles for collection, processing, analysis and reporting of data are given in the periodic reports published by NCRP[1]. The same reports also provide the definitions of different terms used, aspects of coding as per the International Classification of Diseases for Oncology (ICD-O)[2], statistical calculations used for population estimations as well as that for incidence and mortality rates.

The data collected by the Registries is subjected to various types of quality checks, which included duplicate checks and other consistency checks such as related to age, sex, site of cancer and morphology.

Population. Census data[3] on Ward-wise population was utilized to arrive at total population of MIC affected (Area 1) and MIC un-affected areas (Area 2). The population and the growth rates for the two areas are given in Table 1. Difference distribution method was used to calculate the five yearly age group population estimates for inter-census years[4]. The density of population according to the same census was 4755.46 /Sq. Km.

Registration of cancer cases. The data obtained over the years showed at least sixty three sources of registration of cancer cases. This includes cases registered in sources in Bhopal as well as in major cancer hospitals in the country like Tata Memorial Hospital, Mumbai. Besides the usual checks stated above, further checks for the ward codes were done. This was to ensure the correct categorization of the cancer cases into Area 1 and Area 2 respectively.

A random check to validate the residential status was also done through; follow-up of 200 cases from various years. No significant disparity was found in their categorization. Table 14.2 gives the number of cancers registered in the Bhopal PBCR area by area and gender.

"Cancer incidence" refers to the number of new cases of cancer seen in the population of a defined geographic over a definite period of time.

Time trend analysis using simple and join-point regression. The incidence rates for the year 1988 to 2003 were subjected to regression analysis using actual AAR values and slopes were calculated for Area 1 and Area 2, to study whether these rates follow some sort of trends in relation to time. The slopes were calculated for actual data for Area 1 and Area 2. Joinpoint is a statistical software for the analysis of trends using joinpoint models, that is, where several different lines are connected together at the "joinpoints." This software program has been developed and used by the National Cancer Institute, USA.

Table 14.1 Population & Growth rate of MIC/Toxic Gas Affected (Area 1) and MIC Un-affected (Area 2) areas for years 1981, 1991 & 2001

Year	Male		Female	
	Area 1	Area 2	Area 1	Area 2
1981	230256	132730	201606	114220
1991	347386	223381	311387	198648
2001	442994	325396	39750	292520
Average annual growth rate (1981-1991)	4.2	5.2	4.4	5.7
Average annual growth rate (1991-2001)	2.5	3.8	2.6	3.9

Assumptions Used in Analysis

1. All cancer cases reported from the Area 1 were considered as cancer cases in MIC Affected Areas; and all cancer cases coming from Area 2 were considered as cancer cases in MIC Un-Affected Areas. At this stage the two different groups of cancer cases cannot be causally attributed to MIC. However, a close watch should be kept for differences in the prevalence rates and severity of the different types of cancers in the two Areas. In the case of leukaemias which may be seen even earlier, the present data needs to be initially assessed with regard to the type and whether acute or chronic at different periods of time.
2. The cases born after the year 1985 were excluded from the further analysis as they may dilute the true differences existing in the cancer pattern of Area 1 and Area 2.
3. Assumption was made that within each five year age group the populations are uniformly distributed in the two areas.

RESULTS

Comparison of Incidence Rates in Area 1 and Area 2

Table 14.3 gives the crude (CR) and age adjusted incidence rates (AAR) over the years (1988-2003) for the two areas in males and females. The last two rows give the value based on the Wilcoxon test and the significance (p-value) of these rates based on comparison

between the two areas. Among males there is a significant difference between the two areas with the affected area showing a significantly higher incidence rates, whereas there is no such difference in females.

Table 14.4 gives similar values for leading sites of cancer in males and females.

Table 14.2 Number of Cases Over Years by Sex and Area – Bhopal – (1988-2003)

Year	Area 1		Area 2	
	M	F	M	F
1988	165	137	84	94
1989	183	160	97	79
1990	199	176	95	103
1991	208	180	113	104
1992	205	184	128	122
1993	210	178	141	138
1994	234	190	141	144
1995	288	195	162	130
1996	240	196	159	163
1997	248	208	174	178
1998	247	204	181	169
1999	280	220	173	181
2000	287	233	184	192
2001	293	234	199	202
2002	317	263	202	212
2003	322	284	229	210

Leading sites in males. Cancer of tongue, mouth, hypopharynx, oesophagus and lung showed significantly higher incidence rates in Area 1 as compared to Area 2.

Leading sites in females. Cancer of mouth and cervix showed significantly higher incidence rates in Area 1 compared to Area 2. However, the reverse was observed for cancer breast where-in in Area 2 showed significantly higher rate.

Time Trend in Incidence Rates (AAR) of Area 1 and Area 2

The leading sites of cancer for either sex with statistical results of slope (b), SE. (b), t values and p-values over time for Area 1 and Area 2 were calculated based on linear regression and join-point regression models for both males and females.

Cancer of all sites of males and females showed a significant increasing trend in incidence rates over the years in Area 1 by both the Linear Regression (LRM) and Joinpoint Regression method (JPRM), while in Area 2 no linear trend was observed.

Among the leading sites in males in Area 1 cancer of the larynx showed an increasing trend while cancer of the stomach showed a decline. In Area 2 no such change was seen in these sites of cancer. However cancer of the prostate showed an increasing trend.

Among the leading sites of cancer in females, cancer of the gall bladder showed an increasing trend in Area 1 but not in Area 2. Cancer of the breast showed an increasing trend in only Area 2. Likewise cancer of the cervix showed a declining trend only in Area 2.

Table 14.3 Comparison of Crude (CR) and Age Adjusted Incidence Rates (AAR) for All Sites of Cancer for Area 1 and Area 2 - Bhopal- Males and Females-(1988-2003)

Year	Males				Females			
	CR		AAR		CR		AAR	
	Area 1	Area 2	Area 1	Area 2	Area 1	Area 2	Area 1	Area 2
1988	54.24	44.27	95.86	87.76	50.80	55.61	89.56	95.95
1989	59.22	49.46	105.26	91.04	57.98	45.49	97.95	78.83
1990	62.92	46.85	110.70	83.99	62.15	56.96	94.32	89.69
1991	66.32	55.22	114.02	99.51	64.18	56.99	102.92	89.81
1992	65.36	61.93	114.68	104.34	65.36	66.08	104.96	100.30
1993	67.09	67.27	114.16	111.12	63.34	73.58	101.91	110.29
1994	74.87	66.41	124.11	109.29	67.81	75.96	107.40	110.92
1995	73.26	74.96	122.29	119.52	69.59	67.33	112.29	101.25
1996	77.23	72.19	127.72	119.09	70.01	82.83	113.71	120.00
1997	80.18	78.02	130.29	122.49	74.49	88.80	120.73	126.06
1998	80.21	79.72	132.92	122.49	73.28	83.20	114.43	114.85
1999	91.35	75.22	150.95	114.60	79.53	87.76	124.97	118.86
2000	94.32	78.75	148.31	123.78	84.43	91.46	132.30	122.25
2001	96.84	83.81	155.25	122.88	85.26	94.53	133.66	126.79
2002	105.58	84.06	161.61	126.59	96.03	97.89	150.57	126.39
2003	108.33	94.18	162.29	129.96	95.60	96.07	144.80	113.54
Wilcoxon Z		3.309		3.516		-1.862		1.810
P value		0.001		0.000		0.063		0.070

DISCUSSION

Cancer patterns vary not only throughout the world but also between different population groups within the same country[1,5-7]. The preliminary and subsequent reports of the NCRP has shown, cancer of the stomach as a consistent leading site of cancer among males in Bangalore and Chennai, whereas it is lower down among the leading sites of cancer in Bhopal, Delhi or Mumbai. Similarly, cancer of the gall bladder is a leading site of cancer especially among women in Bhopal and Delhi, but is hardly seen in Bangalore and Chennai.

Studying the magnitude and patterns of cancer would be the first step in determining clues to the cause of cancer and having a baseline to plan and assess control measures. Epidemiologic studies based on these help in knowing what is happening and what can be done about it. Cancer registries provide the needed information to undertake such investigations.

Over the years, the registries under the NCRP have provided valuable and reliable scientific data on cancer. The Bhopal PBCR was set up as a special purpose PBCR to observe the differences in cancer patterns and trends in incidence rates of cancer in the population exposed to the methyl-isocyanate (MIC)/toxic gas and those not exposed.

The NCRP has under its network evolved standard methods of data collection, quality checks, processing, analyzing and reporting[8]. These activities are coordinated, monitored and assisted by the Coordinating Unit of the NCRP at Bangalore. Data on incidence rates obtained through active registration are reasonably complete[9] and have been accepted for publication internationally[10,5-7]. There have been limitations in the completeness of mortality data, but this is also being overcome by following back all the recorded deaths in the registry area regardless of cause of death.

Table 14.4 Comparison of CR and AAR between Area 1 and Area 2 of Bhopal-Males - (1988-2003)

Male	CR		AAR	
	Z value	**P-value**	**Z value**	**P-value**
All sites	3.309	0.001	3.516	0.000
Tongue	3.464	0.001	3.464	0.001
Mouth	2.585	0.010	2.741	0.006
Hypopharynx	1.913	0.056	0.056	0.025
Oesophagus	2.741	0.006	2.844	0.004
Stomach	0.259	0.796	0.103	0.918
Larynx	1.344	0.179	0.672	0.501
Lung	2.100	0.034	2.379	0.017
Prostate	-1.241	0.215	-0.983	0.326
Brain NS	-1.448	0.148	-1.655	0.096
NHL	1.079	0.281	0.227	0.820
Myeloid leukaemia	-0.824	0.410	-0.170	0.865
Female		CR		AAR
	Z value	P-value	Z value	P-value
All sites	-1.862	0.063	1.810	0.070
Mouth	1.293	0.196	2.689	0.007
Oesophagus	1.706	0.088	1.939	0.052
Stomach	0.155	0.877	0.289	0.796
Gall bladder	-1.629	0.103	-1.241	0.215
Lung	-1.344	0.179	-0.776	0.438
Breast	-3.516	0.000	-3.464	0.001
Cervix	2.792	0.005	3.361	0.001
Corpus uteri	0.491	0.623	0.724	0.469
Ovary	-1.655	0.098	-1.034	0.301
Brain NS	-0.621	0.535	-0.543	0.587
Myeloid leukaemia	0.170	0.865	0.966	0.334

CONCLUSIONS

The data on patterns and trends of cancer in the Bhopal PBCR have shown some differences between the population in the areas exposed to the gas and those that were not exposed. The higher incidence rates of sites of cancer in the gas affected area are all those anatomical sites that are associated with use of tobacco. Such differences could be due to confounding factors as there are variations in the tobacco habits and socio-economic status of the population in the two areas.

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