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)

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TECHNICAL REPORT
CLINICAL STUDIES

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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.

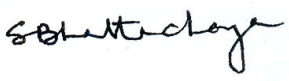
It took a couple of months to register cohorts, prepare study designs and protocols, train field workers, carry out validation tests, before epidemiological data started pouring in. Finally, the population-based long term epidemiological studies from 1985 through 1994 were completed, and the Technical 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.



S.K. Bhattacharya

Addl. Director General

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, An estimated population of over 5 lacs (out of a total of 8 lacs) 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 presented here.

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

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 and 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 value. 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 and 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.

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 60 % males and 90% females 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. 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.

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

Chapter 4

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

Objectives

To 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, with the 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 4^{th} 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..

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%.

II. 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: $VEmax_{50\% \text{ and } 75\%}$ 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%.

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 2^{nd} 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 3^{rd} and 4^{th} 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.

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 evaluate different 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-1985-1986

Oxygen 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 irreversibly N-Carbamoylation 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.

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.

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.

Chapter 10

Health effects of MIC / toxic gas in children:
i) Follow-up studies in children 0-5 years of age at the time of exposure
ii) 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 from 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.

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 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.

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 showed a further reduction of mean cell density. Eleven (30.55%) of the 36 cases had polymegathism of which 9 (25%) showed guttata and 3 (8.33%) had pigments, sharing higher prevalence 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 ocular changes namely trachoma, chronic irritative conjunctivitis, corneal opacities, cataract–complicated in some cases with polychromatic lustre and fundus abnormalities.

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.

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 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.

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