Briefing Report on Medical Research by Sambhavna Trust

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Introduction

As highlighted in the Deed of the Sambhavna Trust, "The main object of the Trust is the welfare of the survivors of the Bhopal Gas Disaster through medical care, research, health education and information dissemination." In fulfilment of its primary objective the Sambhavna Trust has been actively engaged in epidemiological and clinical research for the benefit of the gas victims and those exposed to contaminated ground water. The unprecedented magnitude and nature of toxic exposure, unexpected long term consequences and the lack of knowledge on appropriate therapeutic interventions make medical research in Bhopal imperative both for generating knowledge and for developing treatment methodologies. Despite the involvement of ICMR in 24 medical research projects for 10 years, there are vast knowledge gaps that require to be filled for a better understanding of the consequences, their management and for possible precautionary measures to be taken to minimize some of the long term health problems. Prior to the disaster there was only one research paper on the health impact of Methyl Iso Cyanate (MIC) exposure published in a peer reviewed international journal and it is rather unfortunate that there is still a paucity of such publications. Accessibility to findings of medical research continues to remain an issue of concern and due to lack of coordination between medical research and medical treatment the benefits of medical research have not reached the survivors with chronic illnesses. Despite financial and other resource constraints, Sambhavna Trust has carried out epidemiological and clinical studies following ethical norms and published some of them in international peer reviewed journals. The clinic run by the Trust has the space, trained scientific personnel, experience of carrying research in community as well as in the clinic and access to expertise and institutions.

Research at Sambhavna

In accordance with its Deed, the Sambhavna Trust has invested significant part of its resources into medical research likely to contribute towards "welfare of the survivors of the Bhopal Gas Disaster." The epidemiological and clinical research studies carried out at Sambhavna, as well as the ongoing research projects are broadly directed towards identifying long term, including trans-generational, health impacts of toxic exposure and assessing therapeutic efficacy of safer medical interventions. A list of research carried out till date is presented in Table 1. More recently with greater emphasis being paid to other aspects of scientific research as well as appointment of staff trained in microbiology, research areas of Sambhavna have been expanded to include microbiological research as well as research towards improvement of quality of medicines and environmental safety as is apparent from the summary of ongoing research projects presented in Table 2.

A total of six research activities have been conducted at Sambhavana trust and another eight research activities are ongoing. From these research activities, three articles have been published in indexed international journals and another four articles are in developmental stage.

Table 1 : Research Carried out by Sambhavna Trust

S No.	Title	Year	Population	Parameters	Finding	Outcome
1.	Effects of Yoga practices for respiratory disorders related to the Union Carbide Gas Disaster in 1984.	1999	30 persons with respiratory disorders following gas exposure	Spirometry values Pulse & Respiratory rates.	Yoga can lead to sustained improvement in lung functions of exposed persons with chronic respiratory problems.	Yoga instructors trained by Sambhavna Trust are providing care in two government hospitals
2.	Effect of parental exposure on children.	2001	141 children of exposed and unexposed parents	Anthropomorphic values.	Male children of exposed parents are thinner, lighter and have smaller cranial circumference compared to male children of unexposed parents.	Publication in Journal of the American Medical Association
3.	Long term follow up of persons exposed to toxic gas in-utero.	2006	141 children of exposed and unexposed parents	Anthropomorphic values. Tanner stage	Early stunting among male children of exposed parents is followed by a catch-up growth.	Publication in Journal of the Federation of American Societies for Experimental Biology
4.	Anemia prevalence in communities exposed and unexposed to contaminated ground water.	2007	300 adults exposed and 303 adults unexposed to contaminated ground water.	Haemoglobin levels.	Average Hb concentration of men exposed to contaminated groundwater was shown to be almost 1g/dL lower than that of men with access to clean water.	Follow up study required with appropriate sample size.
5.	Comparative efficacy of Yoga therapy in treatment of Dysmenorrhoea of women exposed to	2008	60 women with Dysmenorrhoea	Menstrual pattern Severity of pain	Yoga was found to be more effective than pain killers.	Yoga therapy included in protocol for treatment of Dysmenorrhoea.

	contaminated ground water.					
6.	An epidemiological cross-sectional study of the effects of exposure to toxic gases and contaminated water on the Bhopal population.	2010	110, 000 persons in four exposure categories	1. Physical Growth and Mental and Social development milestones for 0 to 5 years old.children, 2. Mid arm circumference, Cranial circumference, Leg length, sitting height, standing height and weight of 2 to 15 years old children, 3. Mortalities between January 1, 2006 till survey date for all four populations.4. Mortalities between December 3, 1984 and December 31, 1989 for gas exposed population, 5. Reproductive history of all women, 6. Diagnosed Cancers, 7. Diagnosed Tuberculosis, 8. Diagnosed Paralysis and 9. Congenital abnormalities	Preliminary findings indicate that in comparison to unexposed families, gas and contaminated ground water exposed families have significantly larger number of people with TB, paralysis and cancers. Lung, abdominal, throat and oral cancers are significantly higher in gas exposed and gas plus contaminated ground water exposed group. Gas exposed women were found to have suffered significantly larger number of abortions in comparison to unexposed women. Compared to an unexposed population, significantly larger number of children born to gas exposed and contaminated ground water exposed parents had birth defects.	To be sent for publication after final data analysis is over.

Table 2: Summary of Ongoing Research Work in Sambhavna Trust Clinic in May 2018

S No.	Title	Objective	Methodology	Participants	Current Status	Completion date	Follow up
1.	Comparison of status of health and healthcare of gas affected people with respect to unexposed.	To identify priorities of and improvements required in health care of the gas affected population.	Administration of a field tested questionnaire on a sub sample of the cohort for gas exposed and unexposed individuals.	Tasneem Zaidi, Santosh Kshatriya, Farhat Jahan, Hariom Vishwakarma, Shailendra Chourasia	Data collection over. Analysis of data is ongoing.	May 2018	Report to be forwarded to all agencies involved in health care of gas victims. Hindi report to be distributed among the study population.
2.	Assessment of effectiveness of Ayurvedic treatment in Autoimmune disorders.	Standardize Ayurvedic interventions for Rheumatoid arthritis and Psoarisis	Assessment of effectiveness through Follow up questions and investigations pre and post treatment.	Dr. Mrityunjay Mali	Data collection over.	May 2018	Findings to be published in Ayurveda journal.
3.	Establishment of community based system for surveillance of Births and Deaths.	To establish a self sustaining system of birth and death surveillance that is under the control of the local population.	Bring together interested members of a community and provide information, training and standard formats for recording of information.	Tasneem Zaidi, Santosh Kshatriya, Farhat Jahan, Hariom Vishwakarma, Shailendra Chourasia	Focused group discussion among interested members started in two communities.	Pilot phase to be completed by December 2018.	Expanding area of work and periodic monitoring of the work of community based groups.

4.	Development of herbal preservatives for water based herbal preparations.	To develop safer herbal alternatives to potentially toxic synthetic preservatives such as Sodium benzoate.	Periodic microbiological examination of Areetha (Sapindas Mukorossi) solution following addition of different extracts of Lantana camara.	Vishwamohan Dwivedi, Prachi Gupta	Effects of different extracts of Lantana camara on Areetha aqueous solution is being studied for presence of fungi at periodic intervals.	December 2018.	Will apply for patent on Herbal preservative. Start routine addition in Areetha solution produced at the Clinic. Share technology with Sambhav Enterprises.
5.	Use of microbes captured from forest for increasing productivity of medicinal plants.	To improve soil quality and plant productivity.	Microbes harvested from nearby forests are grown and sprayed on soil. Conditions created for survival and growth of microbes in soil. Productivity is compared with those on untreated matched soil.	Manmohan Yadav, Ratna Soni, Mukesh Kushwaha, Prachi Gupta	Microbe population increased through adding jaggery. Sprayed on test patch. Plant lengths and girths measured. Data collection ongoing.	December 2018.	In case of positive outcome, a booklet describing the work of harvesting microorganisms and using them for increasing productivity in organic farming will be produced and distributed.

6.	Development of herbal mosquito repellants.	Development of safer alternatives to synthetic mosquito re-pellants.	Hand roll and dry dough prepared with powdered mixtures of Van Tulsi (Ocimum americanum), Neem (Azadirchta Indica) and Vasa (Adhatoda vasica) and a binder.	Chandrakanta, Nandkishore, Vishwamohan	Production and testing of incense sticks is ongoing. Developing machinery for mass production of incense sticks.	March 2019	Large scale production for distribution outside the clinic.
7.	Assessment of effectiveness of herbal alternatives to antibiotics in non-healing wounds.	To standardize herbal interventions against resistant microbes.	Monitor condition of wound treated with herbs and corroborate with culture/sensitivity of resistant organism with regard to herb extract.	Dr. Mrityunjay Mali, Ratna Soni, Prachi Gupta	Herbs to be used have been identified. Preparations made to recruit willing subjects.	December 2019	Development of treatment protocol for non-healing wounds. Publication of findings in research journal.
8.	Standardizing herbal alternatives to Fluoconazole for treatment of Fluoconazole resistant candida albicans.	To standardize herbal interventions against resistant fungi.	Monitor condition with treatment with herbs and corroborate with culture/sensitivity of resistant fungi with regard to herb extract.	Dr. Satiwan Mordia, Dr. Usha Arya, Dr. Mrityunjay Mali, Prachi Gupta	Herbs to be used have been identified. Preparations made to recruit willing subjects.	December 2019	Development of treatment protocol for Fluoconazole resistant candida albicans. Publication of findings in research journal.

Research Ethics Committee

Much attention is paid to ethical aspects of medical research at Sambhavna. No information is collected or test carried out on any individual without her / his formal and informed consent. In accordance of the ICMR Guidelines, Sambhavna's 7-member Research Ethics Committee consists of two medical professionals, a lawyer, two social workers and a representative from the community.

Funding of Research at the Sambhavna Trust Clinic

Medical research carried out at the Sambhavna Trust Clinic has largely been funded by small donations from several thousand individual donors sympathetic to the plight of the survivors. Since its inception, the Sambhavna Trust has received a total of Rs. 23, 80, 138 as institutional grants from the Canadian Institute of Health Research and the Memorial University, Canada . While earlier our application for funding an epidemiological study was rejected by the Indian Council of Medical Research, more recently in January 2017 our application for grants from ICMR for a clinical research in Ayurveda titled "Ayurvedic virechana therapy as a means to detoxify persons in Bhopal with history of chronic exposure to chemicals and heavy metals and documentation of consequent changes in their health status" .has been approved subject to our registration with the DSIR as a SIRO.

Beneficiaries of Research by the Sambhavna Trust

The primary beneficiaries of clinical research carried out by the Sambhavna Trust are the 34, 303 patients registered till date for long term care with the Sambhavna Trust Clinic. Clinical research in to therapeutic efficacy of interventions in Ayurveda or Yoga have gone a long way in improving quality of care as well as significantly reduced unnecessary load of synthetic medicines. Upwards of 10 thousand families exposed to bio-accumulative toxins in the ground water in the vicinity of the abandoned factory could potentially benefit from the findings of the proposed study of Ayurvediuc detoxification. Results of the large scale epidemiological study involving 9 parameters is likely to have significant value for over half million survivors of the gas disaster as well as over 50 thousand residents of communities known to be affected by groundwater contamination.

Publication of Research

Following papers based on research work carried out by Sambhavna staff and others are appended in their entirety.

1. Catch-up growth in males affected by the Union Carbide disaster of 1984 in Bhopal, India

Daya R Varma, Ritesh Pal, Diana Katgara, Satinath Sarangi, Tasneem Zaidi, Steven Holleran, Rajashekhar Ramakrishnan and Shree Mulay

Federation of American Societies for Experimental Biology

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2. Effects of exposure of parents to toxic gases in Bhopal on the offspring

S. Sarangi Mtech, T. Zaidi, R.K. Pal, D. Katgara, V.G. Gadag, S. Mulay, D.R. Varma

American Journal of Industrial Medicine

Vol. 53, Issue 8, August 2010, pp. 836 - 841

3. Methyl Isocyanate Exposure and Growth Patterns of Adolescents in Bhopal.

Nishant Ranjan, Satinath Sarangi, V T Padmanabhan, Steve Holleran, Rajshekhar Ramakrishnan, Daya R Varma

Journal of American Medical Association

Vol. 290, No. 14, October 8, 2013 pp 1856-1857

Annexures

Pharmacology/Experimental Therapeutics

Catch-up growth in males affected by the Union Carbide disaster of 1984 in Bhopal, India

Daya R Varma, Ritesh Pal, Diana Katgara, Satinath Sarangi, Tasneem Zaidi, Steven Holleran, Rajashekhar Ramakrishnan, and Shree Mulay

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Abstract

Our 2001 study found that exposure of toddlers and parents in Bhopal to toxic gases in 1984 caused stunting of boys but not of girls (JAMA, 290:1856, 2003); here we report on a follow-up study of anthropometrics in 2006. Informed consent of all subjects was obtained. Data were analyzed by two-way ANOVA with the factors exposure (yes, no) and age (born before, in utero, born after), and their interaction, followed by pairwise contrasts of each exposed group with its control. There was a significantly greater increase from 2001 to 2006 in height (mean±SD in cm) of boys exposed to gases as toddlers (5.1± 5.3, n=25, $p<0.05$) vs controls (1.2±2.6, n=14), or born to exposed parents (15.5±7.8, n=6, $p<0.01$) vs controls (7.4±4.0, n=7), resulting in nearly complete catch-up; also, body weight and mid-arm circumference increased significantly more in exposed than in control males. There was a significant correlation in 2001 for height versus age in boys but not in girls, suggesting that the growth deficit found in exposed boys in 2001 was not present in girls because the girls attained their full height at a younger age. The mechanism underlying early stunting followed by a catch-up growth is unclear. An important adverse effect of the Bhopal disaster was lasting pulmonary

pathology. The catch-up growth in these boys might be similar to that observed in asthmatic children. (Supported by the Canadian Institutes for Health Research)

Figures References Related **Details**

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Effects of Exposure of Parents to Toxic Gases in Bhopal on the Offspring

S. Sarangi, MTech,[1] T. Zaidi, BA,[1] R.K. Pal, MCom,[1] D. Katgara, BSW,[1] V.G. Gadag, PhD,[2] S. Mulay, PhD,[2] and D.R. Varma, MD, PhD[3]*

Background *Exposure to methyl isocyanate and other toxic gases in Bhopal, India, on December 3, 1984 resulted in thousands of acute deaths, pregnancy loss and long-term effects.*

Methods *From 1985 to 2007, we conducted successive surveys of vital status and health to determine whether the exposure of parents to toxic gases in the Bhopal incident affected the 5-year survival and anthropometric variables of their offspring.*

Results *Initial 5-year mortality of offspring of exposed parents was very high. Male but not female offspring who were exposed to gases in utero or who were born to exposed parents were stunted in growth until puberty, which was followed by a period of accelerated growth. Results also suggest a post-puberty effect on head circumference of females exposed to gases in utero.*

Conclusion *Exposure of pregnant women to toxic gases in Bhopal in 1984 resulted in high pregnancy loss, increased first 5-year mortality and delayed development of male progeny.*

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KEY WORDS: methyl isocyanate; infant mortality; catch-up growth; Union Carbide Pesticide Plant; Tanner score; pregnancy loss; peak expiratory flow rate; growth stunting

INTRODUCTION

Just past the midnight of December 2–3, 1984, approximately 40 metric tons of methyl isocyanate (MIC) and other toxic gases escaped from the Union Carbide Pesticide Plant in Bhopal, India, within a period of 45–60 min resulting in over 5,000 acute deaths and long-term effects in thousands of survivors [Varma, 1986; Bucher, 1987; Kamat et al., 1992; Vijayan and Sankaran, 1996; Dhara and Dhara, 2002; Varma and Mulay, 2006]. At the time of the Bhopal disaster, it was conjectured that the high chemical reactivity of MIC would result in its destruction upon contact with body surface and no systemic toxicity would follow [Varma, 1986]; this speculation and anecdotal reports of cyanide rather than MIC poisoning greatly influenced both clinical and experimental studies [Varma, 1986; Varma and Mulay, 2006].

We hypothesized that because lungs provide extensive surface area for absorption of gases, MIC is likely to enter the systemic circulation despite its high chemical reactivity and exert systemic effects including effects on pregnancy. To test our hypothesis, we conducted a survey of 3,270 households adjacent to the Pesticide Plant in September 1985 [Varma, 1987]. In these household, 865 women reported to have been pregnant at the time of the gas leak but only 486 of them gave birth to live babies, which amounted to 43.8% pregnancy loss [Varma, 1987]. Another study of 2,566 pregnant women from 18,978 households also found pregnancy loss in 23.6%

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women as compared with 5.6% in 1,218 control cohorts [Bhandari et al., 1990]. Exposure of expectant mothers to toxic gases also resulted in a decrease in placental and fetal weights [Kanhere et al., 1987]. These data were strongly suggestive of an effect of toxic gases on the mother and/or her fetus and have been confirmed in animal studies [Schwetz et al., 1987; Varma et al., 1987].

The present study concerns 5-year survival as well as pre- and post-puberty anthropometric data on boys and girls exposed to toxic gases in utero using unexposed cohorts as well as their older and younger siblings for comparison. An earlier study of a random sample of subjects [Ranjan et al., 2003] had found that boys, but not girls, exposed to gases in utero or born to gas-exposed parents were significantly shorter than their unexposed control cohorts. However, data by Ranjan et al. [2003] were collected in 2001 when the mean age of subjects was 17 years (range 14–19 years). Although the survey had 37 gas-exposed boys, 28 of the gas-exposed subjects were exposed as toddlers, six were conceived to exposed parents and only three were exposed in utero. Here, we report anthropometric data from a follow-up of the earlier study [Ranjan et al., 2003] as well as from additional in utero-exposed males and females and their siblings. The follow-up data were collected from mid-November 2006 to mid-January 2007 (termed 2007 here).

MATERIAL AND METHODS

Study Population and Survey Methods

This study was approved by the Ethics Committees of the Faculty of Medicine, McGill University, and Sambhavana Trust Clinic, Bhopal. Informed consent was obtained from all respondents on a form in *Hindi* script either in writing or by thumb impression. All subjects in this study except the control cohorts lived within 1 km northeast of the Union Carbide Pesticide plant at the time of the accident. This area was in the down wind direction of the escaping gases from the plant and recorded a death rate of more than 3% (150 times the normal rate) within a week of the accident [Varma, 1986; Kamat et al., 1992].

Identity of all subjects was verified on the basis of our records of the first survey conducted in 1985 [Varma, 1987] and the identification number allotted by the Indian Council of Medical Research. This report is based on five surveys as indicated in the flow-chart (Fig. 1). The first, second and the third surveys were performed 10, 21 and 56 months after the accident, which approximately corresponded to infants ages of 1 month, 2 years and 5 years. These three surveys were administered by high school graduates familiar with the area. It was in the immediate aftermath of the disaster and every precaution was taken to explain that the study was of no material benefit to the victims. The surveyors were from the area and cognizant of cultural sensitivity of the population.

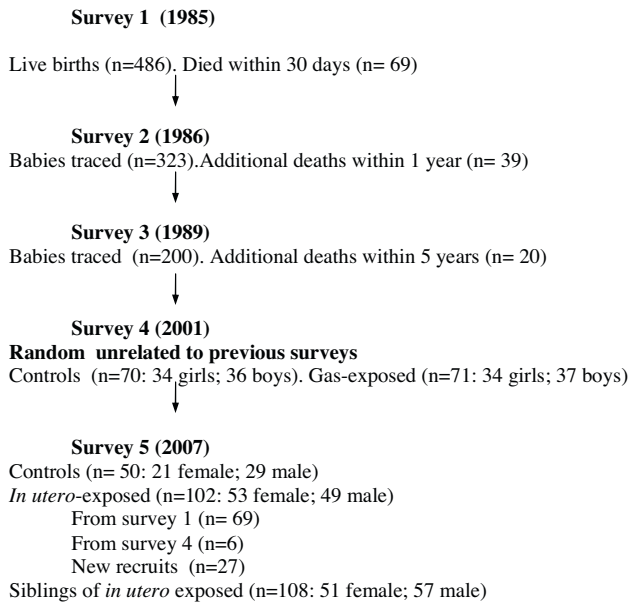

FIGURE 1. Flow-chart indicating details of survey dates and number of subjects.

Surveying students were instructed to record accurately responses without cross-examining the subjects.

The first survey included 3,270 households and was designed to record the outcome of pregnancy and infant mortality within 1 month of age. As mentioned above, these households were selected because they were located adjacent to the Union Carbide Pesticide Plant and in the down wind direction of the escaping gases and a convenient source of locating a large cohort of gas-exposed population. A detailed description of the survey method has been previously reported [Varma, 1987]. Briefly, all subjects were approached by the survey team in person at their homes. On the first encounter, surveyor obtained the consent and fixed an appointment for another meeting to complete the survey questionnaire and record anthropometric data. No household refused to volunteer the information sought although a few subjects did not agree to participate in the Tanner score study as indicated in Tables II and III. No one had moved away from their homes following the accident at the time of the first survey. Households which abandoned their original homes later on are indicated in Table I, columns 3 and 4. No physical examination or laboratory tests were performed to confirm the information on the status of pregnancy volunteered by the subjects.

The second and third surveys were performed 2 and 5 years after the accident to record survival of the children identified in the first survey as well as record the possible cause of death. In these and all other surveys, the follow-up was based on door-to-door visit. The fourth survey was carried out between May 10 and June 30, 2001. In this survey, anthropometric data were collected from adolescents

exposed to gases as infants or born to gas-exposed parents as well as age- and sex-matched unexposed controls [Ranjan et al. 2003]. The cohorts of this fourth survey were unrelated to the first three surveys. The last survey was performed between mid November 2006 and mid-January 2007 (termed 2007 here). This last survey was a follow-up of the subjects of the 2001 survey (fourth survey), but also included additional cohorts (Fig. 1). The respondents understood that the study was of no material benefit to them.

It is not customary in India for people to abandon their ancestral home. However, the Bhopal situation was greatly altered as a result of the disaster, government policy and compensation, and as a result many households moved out. We made the best efforts to trace as many households as we could. In many instances, one whole day was spent locating just one person and make an appointment for a second visit to elicit responses to a questionnaire and record anthropometric data.

In the last survey, all female subjects were interviewed and examined by female staff and male subjects by male or female staff. The subjects of this study included children exposed to gases in utero and controls and their younger and older siblings.

Data Collection

Anthropometric measurements were made as described before [Ranjan et al., 2003]. In addition, peak expiratory flow rate (PEFR) was measured using a mini-Wright peak flow meter (Alliance Tech Medical, Granbury, TX). Subjects were asked to exhale into the mouth piece as quickly and forcefully as they could. This was repeated thrice and the highest reading was used for the analysis. PEFR data were adjusted for age and height [Nunn and Gregg, 1989] and normalized against our controls.

In addition, a follow-up of all subjects of the 2001 survey [Ranjan et al., 2003] was carried out to verify the status of those found stunted in the previous survey. Of these subjects, three born before the disaster and five unexposed controls could not be traced. Of the 180 children who were alive and located 5 years after birth, only 69 could be located in the 2007 survey (Fig. 1). The remaining 33 in utero-exposed children included in this study had identical history and were identified for the first time. Younger and older siblings of the in utero-exposed group of children were used for comparison with in utero-exposed children to minimize effects of socio-economic and genetic factors. However, as the older siblings lived with their parents at the time of the disaster, they were also exposed to toxic gases as infants or toddlers and the younger siblings were born to gas-exposed parents. Therefore, completely unexposed controls were also included. These controls lived in areas farther away from the Union Carbide factory, opposite the wind direction at the time of the accident.

Statistical Analysis

Data were analyzed using SPSS version 15.0 (Chicago, IL). ANOVA was used to compare three or more groups, which were considered independent with respect to exposure. Experiment-wise level of significance was set at 5%. Test-wise type one error was adjusted according to Bonferroni's method.

RESULTS

First 5-Year Infant Mortality

Of the 486 live births, which constituted the follow-up studies, 128 died within the first 5 years (Table I). As all surviving children could not be traced in the succeeding surveys, the total death toll is likely to be higher than that being reported here. The response of the parents to our enquiry about the cause of deaths was not sufficiently specific. In most cases, parents attributed deaths to poor appetite, diarrhea and fever. Difficulty in breathing was not reported by parents as the cause of death in any instance. Female to male ratio of live children at birth was 1.07. However, female to male 5-year mortality was 1.8.

Stunting and Catch-up Growth

This part of the study was based on a very small number of in utero-exposed girls and boys. There was a significantly greater increase from 2001 to 2007 in body weight, height and arm circumference of boys exposed to gases than of controls so that the 2007 height of boys exposed in utero (161.1 ± 8.2, $n = 3$) or born to gas-exposed parents (161.2 ± 6.2, $n = 6$) was no more significantly lower than the

TABLE I. The First 5-Year Mortality in Children Born to Women Exposed During Pregnancy to Toxic Gases in Bhopal on December 3, 1984

Variables	One month after birth [Varma, 1987]	One year after birth	Five years after birth
Household surveyed (n)	3,270	2,622[a]	1,475[a]
Women pregnant during disaster (n)	865	638[a]	374[a]
Live babies born (n)	486	323[a]	200[a]
Infant deaths (n)	69	39	20
Cumulative infant mortality (n)[b]	69	108	128
Cumulative infant mortality (%)	14.2[c]	22.2	26.3
Female/male mortality ratio[d]			1.8

[a]Who could be traced.
[b]Any deaths in untraced subjects are not known.
[c]Infant mortality in the first 30 days after birth in the preceding 2 years in the same households was 3%.
[d]Female to male ratio at birth was 1.07.

TABLE II. Anthropometric Data From 2007 Survey of Females Exposed In Utero to Toxic Gases in Bhopal and their Older and Younger Siblings

	Female	Female	Female	Female	Female
Variable	**Control (n = 21)**	**In utero-exposed (n = 53)**	**Older siblings (n = 31)**	**Younger siblings (n = 20)**	**Younger and older siblings combined (n = 51)**
BW (kg)	46.9 ± 7.2 (43.6–50.1)	41.0 ± 6.2* (39.3–42.17)	45.5 ± 8.8 (42.3–48.8)	48.6 ± 8.1 (44.8–52.4)	46.7 ± 8.6 (44.3–49.1)
Height (cm)	151.8 ± 6.5 (148.8–154.7)	150.6 ± 5.0 (149.2–151.9)	154.2 ± 6.6 (150.6–155.6)	152.0 ± 6.1 (151.1–157.3)	153.5 ± 6.6 (151.7–155.4)
Mid-arm cir. (cm)	23.6 ± 2.6 (22.4–24.8)	22.3 ± 2.1 (21.8–22.9)	23.0 ± 2.5 (22.1–23.9)	24.0 ± 2.6 (22.8–25.2)	23.4 ± 2.5 (22.7–24.1)
Head cir. (cm)	51.7 ± 4.2 (49.8–53.6)	51.1 ±3.8 (50.1–52.1)	52.8 ± 2.1 (52.0–53.5)	53.3 ± 1.2 (52.7–53.8)	53.0 ± 1.8 (52.5–53.5)
BMI (kg/m^2)	20.3 ± 2.7 (19.1–21.6)	18.0 ± 2.7 (17.2–18.7)	19.4 ± 3.5 (18.1–20.7)	20.5 ± 3.9 (18.7–22.4)	19.8 ± 3.7 (18.8–20.9)
Tanner < 5 (% of n)	26.3 (19) (6.5–46.1)	67.3 (52) (54.6–80.1)	21.4 (28) (6.2–36.6)	100 (18) (100–100)	52.2 (46) (37.7–66.6)
PEFR (L/min)	318 ± 32 (303.6–332.4)	259 ± 41 (247.9–270.1)	262 ± 54 (242.0–282.0)	265 ± 79 (228.5–301.5)	263.2 ± 64.9 (244.4–281.9)

Circ, circumference; BMI, body mass index; PEFR, peak expiratory flow rate.
All values are mean ± SD and 95% confidence interval shown in parentheses under the mean values. The numbers of subjects participating in Tanner score study are indicated in parentheses.
*$P < 0.05$, different from all other values in the same row.

height of control cohorts (165.1 ± 5.8, n = 26). However, data were still suggestive of incomplete catch-up of height but the very small sample size does not allow drawing unequivocal inference.

Anthropometric Data on Additional Cohorts

With the exception of body weight, there were no other significant differences in the in utero-exposed females compared with their siblings or unexposed controls (Table II). There was a small but significant ($P < 0.05$) difference in the height of in utero-exposed boys compared with younger siblings or younger plus older siblings combined (Table III). However, when in utero-exposed boys and girls were compared with older and younger siblings of the same sex rather than all the siblings as presented in Tables II and III, head circumference and BMI of in utero-exposed girls was less than that of both older and younger siblings (Table IV).

Tanner Score

Although a higher percentage of in utero-exposed males and females had Tanner scores less than 5, the difference was not significant (Tables II and III).

Pulmonary Function

PEFR values did not differ between in utero-exposed boys and girls and their respective siblings and unexposed controls (Tables II and III). We did not have sufficient resources to conduct other pulmonary function tests.

DISCUSSION

In the immediate aftermath of the Bhopal disaster of 1984, there were two major controversies of clinical significance. The high chemical reactivity of MIC is well known [Varma, 1986; Bucher, 1987]. Indeed MIC was used in Bhopal to make the pesticide carbaryl (Sevin^R) precisely

TABLE III. Anthropometric Data From 2007 Survey of Males Exposed In Utero to Toxic Gases in Bhopal and Their Older and Younger Siblings

Variables	**Control (n = 29)**	**In utero-exposed (n = 49)**	**Older siblings (n = 35)**	**Younger siblings (n = 22)**	**Siblings combined (n = 57)**
BW (kg)	51.5 ± 8.9 (48.1–54.8)	51.3 ± 6.1 (49.5, 53.1)	51.9 ± 7.5 (49.3, 54.4)	45.1 ±7.6 (41.7, 48.5)	49.3 ± 8.2 (47.1, 51.5)
Height (cm)	164.9 ± 6.6 (162.4–167.4)	167.0 ± 6.6* (165.1–168.9)	164.4 ± 7.0 (162.0–166.8)	160.4 ± 7.2 (157.2–163.6)	162.9 ± 7.3 (160.9–164.8)
Mid-arm cir. (cm)	24.1 ±2.8 (23.1–25.2)	24.4 ± 2.1 (23.8–25.0)	25.2 ± 2.1 (24.5–25.9)	22.9 ± 2.7 (21.7–24.1)	24.3 ± 2.2 (23.8–25.0)
Head cir. (cm)	55.0 ± 1.6 (54.4–55.6)	43.3 ± 1.9 (53.7–54.8)	54.4 ± 1.6 (53.8–54.9)	52.7 ± 2.4 (51.7–53.8)	53.7 ± 2.1 (53.2–54.3)
BMI (kg/m^2)	18.8 ± 2.3 (18.0–19.7)	18.4 ± 1.7 (16.5–23.8)	19.2 ± 2.1 (18.4–19.9)	17.5 ± 2.5 (16.4–18.6)	18.5 ± 2.4 (17.9–19.1)
Tanner<5 (% of n)	21.1 (19) (2.7–39.4)	39.6(48) (25.8–53.4)	42.9(35) (26.5–59.3)	47.6(21) (26.3–69.0)	44.6(56) (31.6–57.7)
PEFR (L/min)	456 ± 85 (417.8–494.2)	426 ± 86 (401.7–450.3)	427 ± 96 (395.2–458.8)	361 ±122 (308.8–413.2)	401.5 ± 111.6 (372.3–430.8)

Circ, circumference; BMI, body mass index; PEFR, peak expiratory flow rate.
All values are mean ± SD and 95% confidence interval shown in parentheses under the mean values. The numbers of subjects participating in Tanner score study are indicated in parentheses.
*$P < 0.05$ in utero exposed different from younger and combined siblings.

TABLE IV. Differences Between Anthropometric Data of In Utero-Exposed Group (IUEG) and Their Older Siblings (OS) and Younger Siblings (YS) of the Same Sex

Variables	Female OS − IUEG mean ± SD (n = 15)	Female YS − IUEG mean ± SD (n = 8)	Male OS −IUEG mean ± SD (n = 14)	Male YS − IUEG mean ± SD (n = 11)
Weight (Kg)	3.67 ± 6.3*	4.19 ± 5.1	2.05 ± 6.6	−3.5 ± 7.3
Height (cm)	1.5 ± 3.7	2.0 ± 7.2	−1.7 ± 7.1	−4.0 ± 9.6*
Arm Circ. (cm)	0.41 ±2.6	1.01 ±1.6	1.13 ± 2.8*	−0.92 ± 3.5
Head Circ. (cm)	1.52 ± 5.1*	3.56 ± 6.8*	0.56 ± 1.8	−1.42 ± 3.4
BMI (kg/m^2)	1.48 ± 2.7*	1.48 ± 1.9*	1.07 ± 2.0*	−0.49 ± 2.1

Circ. Circumference; BMI, body mass index.
Number of subjects is different from those in Table III because comparison of the in utero exposed group is made only between older and younger siblings of the same sex. Negative value means that the sibling value is less than that of IUE group.
*$P < 0.05$.

because of its high chemical reactivity [Varma, 1986; Varma and Mulay, 2006]. The controversies were the following: first, given the high chemical reactivity of MIC, can it produce systemic effect or will its effects be limited to exposed surface such as the eye [Andersson et al., 1984]? Second, was MIC or hydrogen cyanide (HCN) responsible for the deaths and long-term effects in Bhopal [Varma, 1986]?

There is evidence that despite the presence of dozens of residues in the Tank #610 from which MIC escaped [Varma, 1986], the main culprit for the short- and long-term effects was MIC and not HCN [Varma, 1989]. Cherry-red venous blood was more probably caused by hemoconcentration rather than as a result of MIC–hemoglobin interaction [Jeevaratnam and Vaidyanathan, 1992]. Furthermore, MIC can cause ocular, pulmonary and other effects notwithstanding its high chemical reactivity [Varma, 1986; Bucher, 1987; Kamat et al., 1992; Vijayan and Sankaran, 1996; Dhara and Dhara, 2002; Varma and Mulay, 2006]. As well, MIC can interact with proteins [Brown et al., 1987], act as a hapten [Karol et al., 1987] and rapidly cross the placenta [Ferguson et al., 1988].

An excessively high pregnancy loss as a consequence of exposure to toxic gases in Bhopal has been previously documented [Varma, 1987; Bhandari et al., 1990]. The 5-year mortality in India is 10.2% [Claeson et al. 2000]. We recorded a minimum of 26.3% 5-year mortality (Table I) in children exposed to toxic gases in utero, which would suggest that fetuses too were affected. It is very likely that some of the pregnancy losses were also caused by fetal developmental defects, which might have manifested as birth defects had they not died in utero. On the other hand, our data do not allow us to identify the cause of in utero deaths and high infant mortality. Parents were unable to attribute deaths to any specific ailment other than poor appetite, diarrhea and fever and did not report difficulty in breathing which could have been suggestive of childhood asthma-like ailment.

A significantly high infant mortality in the first 5 years further indicates that the health of the live-born children was seriously compromised. The female to male ratio at birth of 1.07 is normal and would suggest an absence of gender selectivity in intrauterine deaths; this also suggests that the population living in proximity of the Union Carbide plant did not resort to selective female feticide, quite common in India [Jha et al., 2006]. Whether a higher 5-year female to male mortality ratio of 1.8 was because of a greater neglect of the female child or more severe effect of intrauterine gas exposure on the female than on the male child cannot be answered on the basis of our data.

Our 2001 survey had revealed marked stunting in boys and but not in girls exposed to toxic gases in utero or born to gas-exposed parents [Ranjan et al., 2003]; neither in these cohorts nor in a larger population of in utero-exposed boys or girls we found a significant stunting during the 2007 survey. On the other hand, there was a significant increase in height in exposed males from 2001 to 2007 suggestive of catch-up growth. At the same time, this catch-up growth was more complete in subjects exposed as toddlers than in those exposed in utero or born to exposed parents.

The absence of a significant effect of gas exposure on the height of girls in the 2001 study [Ranjan et al., 2003] could be due to girls attaining their full height at a younger age, as suggested by an absence of correlation between height and age in girls and a significant correlation in boys. It is also possible that there was no significant stunting in girls at any stage of their life, which is suggested by experimental data showing a significantly low body weight of male but not of female mice pups up to 2 months of age when their mothers were treated with MIC metabolite trimethylamine from day 6 to day 15 of gestation [Guest and Varma, 1993]. At the same time, a significantly lower head circumference and body mass index of in utero-exposed girls relative to their older as well as younger sisters (Table IV) is suggestive of a post-puberty retardation in the development of females.

The mechanism underlying early stunting followed by a catch-up growth is unclear. This could have been caused by hormonal imbalance but these were not measured by us in Bhopal cohorts. Exposure to toxic gases in Bhopal in 1984 caused numerous short and long-term effects [Bucher, 1987; Dhara and Dhara, 2002; Varma and Mulay, 2006] including lasting pulmonary pathology [Kamat et al., 1992; Vijayan and Sankaran, 1996]. Childhood asthma can cause early stunting followed by catch-up growth [Russel, 1994; Doull, 2004]. However, our PEFR data (Tables II and III) are not suggestive of any significant compromise in pulmonary functions.

In conclusion, our data are suggestive of delayed growth of the male until puberty and some slowing of growth of the female after attaining puberty. We are following reproductive performance and gender-related variable of females who were exposed to the toxic gases in utero.

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eficial in patients with diabetes mellitus. Further research is clearly needed to understand how and why, as reported by Tsalamandris et al, some patients with diabetes lose renal function in the absence of albuminuria.

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RESEARCH LETTER

Methyl Isocyanate Exposure and Growth Patterns of Adolescents in Bhopal

To the Editor: More than 200 000 people were exposed to methyl isocyanate (MIC) and other gases following the Union Carbide (UC) Pesticide Plant incident at Bhopal, India, on December 3, 1984; in addition to thousands of deaths from acute exposure, this incident has resulted in chronic health problems.[1-3] We measured the effects of exposure to fumes from the incident on the physical growth pattern of adolescents.

Methods. Between May 10 and June 30, 2001, we made anthropometric measurements in exposed adolescents as well as in age- and sex-matched unexposed individuals.

The exposed individuals lived within 1 km northeast of the UC plant at the time of the incident; this area recorded a death rate of more than 3% (150 times the normal rate) within a week of the incident.[4] The unexposed individuals lived in localities 15 km southwest or 4 km northwest of the factory; these areas were not affected because of the distance and wind direction. Households for survey were chosen randomly; all identified households except 2 provided written informed consent to participate in the study.

The survey team led by a social worker was from a different town and had no prior knowledge of the health of the adolescents. The team recorded body weight, height, sitting height, mid-arm circumference, head circumference, and triceps skinfold of the adolescents, as well as the height, weight, and socioeconomic status of their parents. Ages were based on birth certificates if available, and otherwise on a "people's calendar" relating to important local events/festivals, horoscopes, parental diaries, and ages of other siblings.

The data were analyzed separately for boys and girls by analysis of covariance with 4 groups (unexposed, postnatal exposure, in utero exposure, and preconception exposure [ie, born after the incident to exposed parents]) and 6 potential covariates: age, mother's height and weight, father's height and weight, and socioeconomic status (per capita monthly income above or below Rs 750 [approximately US $15]). For each outcome variable for each sex, only the covariates that were statistically significant at $P<.05$ were retained in the final model. All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC) using multiple regression, with the 3 types of exposure forced into the model. The number of families with 2 boys (n=6) or 2 girls (n=14) was too small to permit a rigorous analysis of sibling correlation. Instead, analyses were repeated with only 1 child from each family.

Results. The study included 104 families with 68 girls and 73 boys, with 71 of the adolescents exposed to the gases (mean age, 16.9 [SD, 1.3] years) and 70 unexposed (mean age, 16.7 [SD, 1.4] years). The mean (SD) body weights and heights of exposed and unexposed mothers were similar (48.2 [10.1] vs 49.1 [9.0] kg; 149 [5] vs 151 [5] cm), as were those of exposed and unexposed fathers (54.6 [12.3] vs 53.4 [8.9] kg; 163 [6] vs 162 [6] cm). TABLE 1 presents the outcome variables

Table 1. Outcome Variables by Sex, Age, and Exposure to Gases From the Union Carbide Plant Disaster in Bhopal, 1984*

	Girls				Boys			
	Born Before Disaster		Conceived After Disaster		Born Before Disaster		Conceived After Disaster	
Variable	Exposed (n = 20)	Unexposed (n = 16)	Exposed (n = 11)	Unexposed (n = 14)	Exposed (n = 28)	Unexposed (n = 23)	Exposed (n = 6)	Unexposed (n = 8)
Weight, kg	42.1 (6.2)	42.3 (4.3)	38.4 (5.6)	38.2 (5.0)	44.1 (7.7)	46.4 (4.9)	32.6 (2.1)	43.5 (6.6)
Height, cm	148.6 (3.7)	148.5 (5.3)	148.8 (4.7)	148.6 (6.1)	161.2 (9.3)	164.6 (5.0)	145.7 (3.2)	158.8 (7.7)
Sitting height, cm	75.6 (4.3)	76.9 (3.1)	75.8 (4.0)	77.5 (2.9)	80.0 (5.0)	82.7 (2.8)	71.0 (2.5)	78.5 (4.5)
Mid-arm circumference, cm	21.7 (2.4)	21.6 (1.5)	19.8 (1.8)	19.7 (1.2)	20.7 (2.2)	21.9 (1.1)	18.0 (1.1)	20.3 (1.6)
Head circumference, cm	52.1 (1.3)	52.2 (0.9)	51.8 (1.0)	52.3 (1.1)	53.0 (1.7)	53.3 (1.2)	51.3 (0.8)	52.8 (1.2)
Triceps skinfold, mm	11.3 (3.1)	10.4 (3.0)	9.1 (3.3)	8.2 (1.6)	6.5 (2.4)	5.4 (1.4)	5.4 (0.8)	5.7 (1.4)
Body mass index†	19.1 (3.0)	19.2 (1.4)	17.3 (2.3)	17.3 (1.7)	16.8 (1.7)	17.1 (1.6)	15.3 (0.4)	17.2 (1.1)

*All values are mean (SD).
†Calculated as weight in kilograms divided by the square of height in meters.

Table 2. Effect in Boys of Exposure to Gases From the Union Carbide Plant Disaster in Bhopal, 1984

	Postnatal Exposure (n = 28 Born Before Disaster)		In Utero Exposure (n = 3 Exposed as Fetus)		Preconception Exposure (n = 6 Conceived After Disaster)	
Variable	Effect (95% CI)*	*P* Value†	Effect (95% CI)*	*P* Value†	Effect (95% CI)*	*P* Value†
Weight, kg	–2.8 (–5.7 to 0.1)	.06	–10.0 (–16.0 to –3.0)	.003	–7.9 (–13.0 to –2.0)	.007
Height, cm	–3.9 (–7.4 to –0.4)	.03	–13.5 (–21.0 to –6.0)	.001	–8.4 (–15.0 to –1.0)	.02
Mid-arm circumference, cm	–0.9 (–1.7 to –0.1)	.03	–2.7 (–4.6 to –0.8)	.005	–2.0 (–3.5 to –0.5)	.01
Head circumference, cm	–0.09 (–0.8 to 0.6)	.77	–3.2 (–4.8 to –1.5)	<.001	–1.6 (–2.8 to –0.4)	.009
Triceps skinfold, mm	1.0 (0.1 to 1.9)	.03	1.9 (–0.3 to 4.0)	.09	0.3 (–1.3 to 1.9)	.73
Body mass index‡	–0.3 (–0.9 to 0.4)	.46	–1.3 (–2.9 to 0.3)	.11	–1.4 (–2.6 to –0.2)	.03

Abbreviation: CI, confidence interval.
*Effects reported are of each type of exposure on anthropomorphic measures at follow-up, relative to the 36 unexposed boys. Values reported are regression coefficients, equal to the differences between exposed and unexposed boys in Table 1, after adjustment for age, mother's weight, mother's height, father's height, and socioeconomic status. Thus, the effect of postnatal exposure on height is –3.9 cm,.meaning that the boys exposed to the gases were 3.9 cm shorter than unexposed boys of the same age and with the same parental weight and height; the difference in Table 1 is –3.4 cm before adjustment. The effect of preconception exposure on weight is –7.9 kg after adjusting the –10.9 kg difference in Table 1 for covariates, meaning that the boys conceived by exposed parents weighed 7.9 kg less than unexposed boys of the same age and parental weight and height.
†For comparison of effects with zero.
‡Calculated as weight in kilograms divided by the square of height in meters.

for the various combinations of exposure and sex. Data for the few individuals who were exposed in utero (exposed: 3 boys, 3 girls; unexposed: 5 boys, 4 girls) were included in the statistical analysis but are not shown in Table 1. There was no significant effect of any type of exposure, including in utero exposure, in girls. However, exposure was associated with significant decreases in most anthropometric measures in boys (TABLE 2). The exposed boys had lower levels of several anthropometric variables, although their triceps skinfold measurements were greater. The exposure effect was most pronounced in boys exposed in utero and least severe in boys born before the incident. The analysis of covariance showed no significant effect of exposure on the growth pattern of girls. Repeating the analyses with only 1 child from each family yielded essentially identical results.

Comment. We found selective growth retardation in boys, but not in girls, who were either exposed as toddlers to gases from the Bhopal pesticide plant or born to exposed parents. The fact that exposed and unexposed girls were virtually identical in all measures suggests that the exposed and unexposed groups were well-matched and that the association observed in boys is truly a result of exposure and not of other unobserved differences in the demographics. The main chemical that escaped from the plant was MIC, which is readily degraded on contact with water and in the body.[1-3] One of the degradation products of MIC is trimethylamine, which has been reported to produce selective growth retardation of male progeny of mice, associated with a decrease in serum testosterone.[5] It is possible that similar hormonal effects were produced by MIC, its metabolites, or other substances.

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