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Chronic Arsenic Toxicity: Clinical Features, Epidemiology, and Treatment: Experience in West Bengal

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ABSTRACT

Chronic arsenic toxicity due to drinking arsenic-contaminated water has been one of the worst environmental health hazards affecting eight districts of West Bengal since the early eighties. Detailed clinical examination and investigation of 248 such patients revealed protean clinical manifestations of such toxicity. Over and above hyperpigmentation and keratosis, weakness, anaemia, burning sensation of eyes, solid swelling of legs, liver fibrosis, chronic lung disease, gangrene of toes, neuropathy, and skin cancer are some of the other manifestations. A cross-sectional survey involving 7683 participants of all ages was conducted in an arsenic-affected region between April 1995 and March 1996. Out of a population of 7683 surveyed, 3467 and 4216 people consumed water containing As below and above 0.05 mg/L, respectively. Except pain abdomen the prevalence of all other clinical manifestations tested (e.g., pigmentation, keratosis, Hepatomegaly, weakness, nausea, lung disease and neuropathy) were found to be significantly higher in As exposed people (water As > 0.05 mg/L) compared to control population (water As level < 0.05 mg/L). The prevalence of pigmentation and keratosis, hepatomegaly, chronic respiratory disease and weakness rose significantly with increasing arsenic concentrations in drinking water. The respiratory effects were most pronounced in individuals with high arsenic water concentrations who

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also had skin lesion. Therapy with chelating agent DMSA was not found to be superior to placebo effect. However, therapy with DMPS caused significant improvement of clinical condition of chronic arsenicosis patients as evidenced by significant reduction of total clinical scores from 8.90 ± 2.84 to 3.27 ± 1.73; $p < 0.0001$. Efficacy of specific chelation therapy for patients suffering from chronic As toxicity has further need to be fully substantiated. However, supportive treatment could help in reducing many symptoms of the patients. Treatment in hospital with good nutritious diet has been found to reduce symptom score in a subset of placebo treated patients in West Bengal during the course of DMSA and DMPS trial. People should be advised to stop drinking As contaminated water or exposure to As from any other source. The various clinical manifestations should be treated symptomatically.

Key Words: Arsenicosis; Non cirrhotic portal fibrosis; Pulmonary fibrosis; Arsenic epidemiology; Dimercapto succinic acid; Dimercapto propane succinate.

INTRODUCTION

Many aquifers in various parts of the world have been found to be contaminated with arsenic (As) at concentration above 0.05 mg/L. Of these the most noteworthy occurrences are in large areas of West Bengal (India) and Bangladesh, Taiwan, Northern China, Hungary, Mexico, many parts of the USA, Chile and Argentina.

Though chronic arsenic toxicity due to drinking of arsenic contaminated water has been reported from many countries, but reports of large number of affected people in West Bengal, India and Bangladesh are unprecedented. In West Bengal, arsenic contamination of ground water has been reported in 777 villages of eight districts. It is suspected that about 6 million people are exposed to arsenic contaminated drinking water (As level > 0.05 mg/L) in 68 blocks of those 8 districts.[1]

A. HOSPITAL BASED STUDY

On the basis of research carried out in the Department of Medicine and Gastroenterology at Institute of Post Graduate Medical Education and Research, Kolkata, since 1984, the clinical characteristics of chronic arsenic toxicity have been delineated.

Pigmentation, keratosis and skin cancer are the clinical manifestations mostly reported earlier as the effect of chronic arsenic toxicity though occurrence of peripheral vascular disease and neuropathy were reported from a few center. On the basis of detailed clinical, laboratory and relevant investigation in the hospital on people drinking arsenic (As) contaminated water for a long time we described that chronic arsenic toxicity produces protean systemic manifestations.[2]

Patients and Methods

A total of 248 patients, mostly coming from rural areas of the 8 districts of West Bengal were studied clinically and by relevant investigations. The arsenic contaminated water (0.05–3.4 mg/L) which they were drinking was drawn from subsoil water by hand pump from varying depths (20–80 m). The patient population also included 20 cases from South Calcutta drinking water containing higher quantity of arsenic (5.05–14.2 mg/L) in subsoil water due to contamination by factory effluent of manufacturing Paris green (copper acctoarsenite). Duration of intake of contaminated water usually varied from 1 to 15 years, but in some cases it was life long. The water arsenic level was determined by Atomic Absorption Spectrophotometry with hydride generation system.[3]

The inclusion criteria were as follows: Typical raindrop pigmentation and/or depigmentation and/or keratosis of skin of body and limbs, and arsenic level above permissible limit (>0.05 mg/L) in the water consumed by these people.

Routine investigations were carried out in 93 cases who could be admitted in the hospital. The investigations included routine blood, urine and stool examination and liver functions tests. Chest X-ray, ECG, Blood sugar, urea, creatinine and viral markers for HBsAg by enzyme linked immunosorbent assay (ELISA). Liver biopsy was carried out in 69 of these patients who had hepatomegaly and gave consent. The degree of portal fibrosis was graded[4] as: grade I—mild fibrosis producing expansion of portal zome; grade II—expansion of portal zone with thin fibrosis extension producing septae; grade III—moderate fibrosis in the portal zone with thick septae; and grade IV—dense fibrosis within the liver with a tendency to pseudolobulation.

Nerve conduction velocity (NCV) and electromyography (EMG) were carried out on 29 patients with neurological symptoms while lung function tests were done on 17 patients having feature of lung disease. Upper gastro-intestinal endoscopy was done on 60 patients suspected to have portal hypertension. Skin biopsy was done on 5 cases suspected to be suffering from skin cancer. Arsenic level in hair, nail and liver was detected by neutron activation analysis while its concentration in water consumed by the patients were estimated by atomic absorption spectrophotometry.[3]

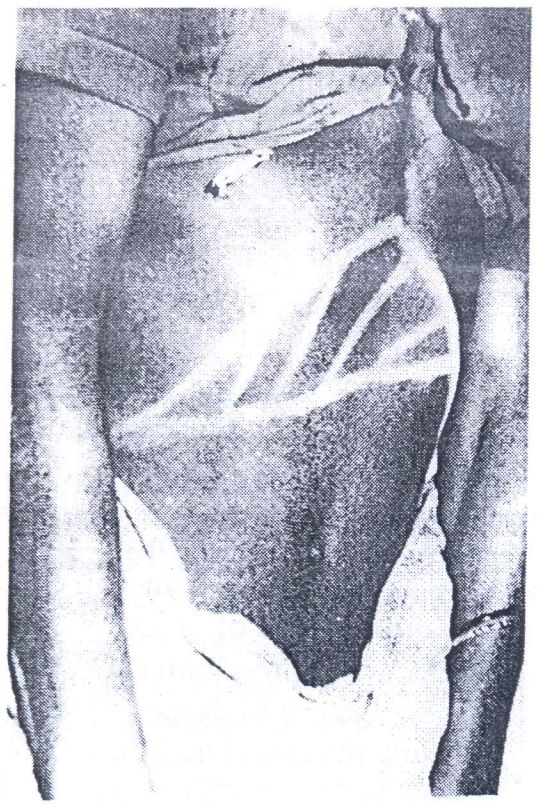
Results

The 248 patients included 193 men, with mean (SD) age 32.5 (13.4) years. The clinical manifestations in these cases are given in Table 1. Pigmentation and keratosis (Fig. 1) were seen in 94.35 and 65.73% of cases respectively while skin cancer was detected in 5 cases. Weakness was a predominant symptom (65.7%) while anaemia was present in 43.9% cases. Symptoms of dyspepsia was present in 66.5% cases. The liver was palpable 2–6 cm below the costal arch in 190 (76.6%) cases, and the spleen 1.5–8 cm below the costal arch in 73 (29.4%) patients; ascites was present in 5 cases. Varices were present in five cases.

Results of liver function tests done in 93 patients with firm hepatomegaly showed elevated ALT (>40 IU/L), AST (>40 IU/L) and alkaline phosphatase ALP (>200 IU/L) in 24 (25.8%), 57 (61.3%) and 27 (29.0%) cases respectively. Serum globulin

Table 1. Clinical characteristics of 248 patients in West Bengal.

	Presenting Features	No. of Patients	Percentage
1	Rain-drop pigmentation	234	94.4
2	Weakness	163	65.7
3	Keratosis (sole & palm)	162	65.3
4	Dyspepsia	165	66.5
5	Cough (± Expectoration)	154	62.1
6	Burning sensation of eyes	74	29.8
7	Anemia	109	44.0
8	Hepatomegaly (firm, Non-tender 2–6 cm below costal margin)	190	76.6
9	Splenomegaly (1.5–8 cm below costal margin)	73	29.4
	Varices (out of 73 cases)	5	
10	Ascites	5	2.0
11	Crepitation ± Ronchi	75	30.2
12	Polyneuropathy	74	29.83
13	Pedal oedema (non-pitting)	23	9.3
14	Peripheral vascular disease (Gangrene)	3	1.2
15	Skin cancer	5	2.0



(*a*)

Figure 1. Clinical features of arsenicosis: (a) Spotty pigmentation of the body with hepatomegaly, (b) Severe keratosis of hand with keratotic horn.

(*b*)

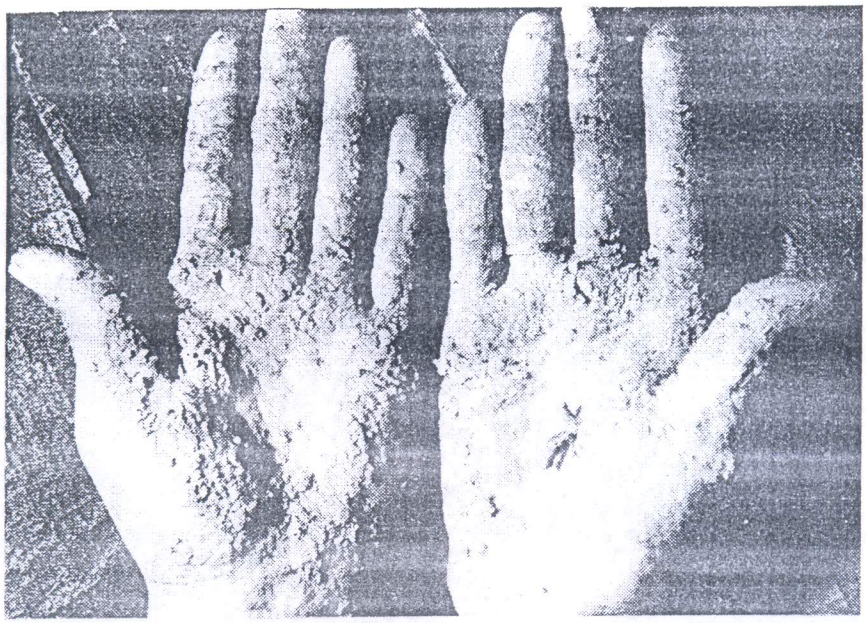


Figure 1. Continued.

level was found high (>3.5 g/dL) in 19 (20.7%) cases. Liver histology showed portal fibrosis in 63 (91.3%) cases, cirrhosis in 2 cases (2.9%) and normal picture in 4 (5.8%) cases. Sera of the two patients with cirrhosis tested positive for HBsAg. The portal fibrosis was characterized by expansion of portal zones of varying degrees. Fibrous extension from the portal tracts into the liver lobules producing septae was found in some cases. At some regions the expanded portal zone contained a leash of vessels replacing the portal vein branches (Fig. 2). The degree of fibrosis in the liver was mild in most patients (grade I in 34 [53.9%], grade II in 19 [30.2%]); moderate to severe fibrosis was observed in only a few cases (grade III in 6 [9.5%] and grade IV in 4 [6.3%]). Portal hypertension was found in 52 cases as evidenced by splenomegaly and/or esophageal varices. However 3 of these patients had hematemesis and melena.

The maximum arsenic content in the liver was 6 mg/kg (mean 1.46 [0.42]; control 0.16 [0.04]; $p < 0.001$), it was undetected in 6 of 29 samples tested. The arsenic content of liver tissue did not correlate with the degree of hepatic fibrosis or with the arsenic content of the water consumed. Undetectable arsenic in 20% of liver samples tested further suggest that fixation of arsenic in the liver tissue may not be permanent. Alternatively, arsenic distribution in liver tissue may not be uniform and there may be sampling error.

Cough with/without expectoration was complained by 62% of patents and clinical examination revealed chest signs in 30% of patients. Chest X-ray showed streaky shadow in some cases suggestive of lung fibrosis (Fig. 3). Lung function tests carried out on 17 patients showed features of restrictive lung disease in 9 (53%) and combined obstructive and restrictive lung disease in 7 (41%). Evidence of polyneuropathy was found in 74 (29.8%) cases. Objective evaluation of neuronal involvement could be done on 29 patients. Of these abnormal EMG was found in 10 (30.8%) and altered nerve conduction velocity and EMG in 11 (38%) cases. Perceptive hearing loss was found in two cases.

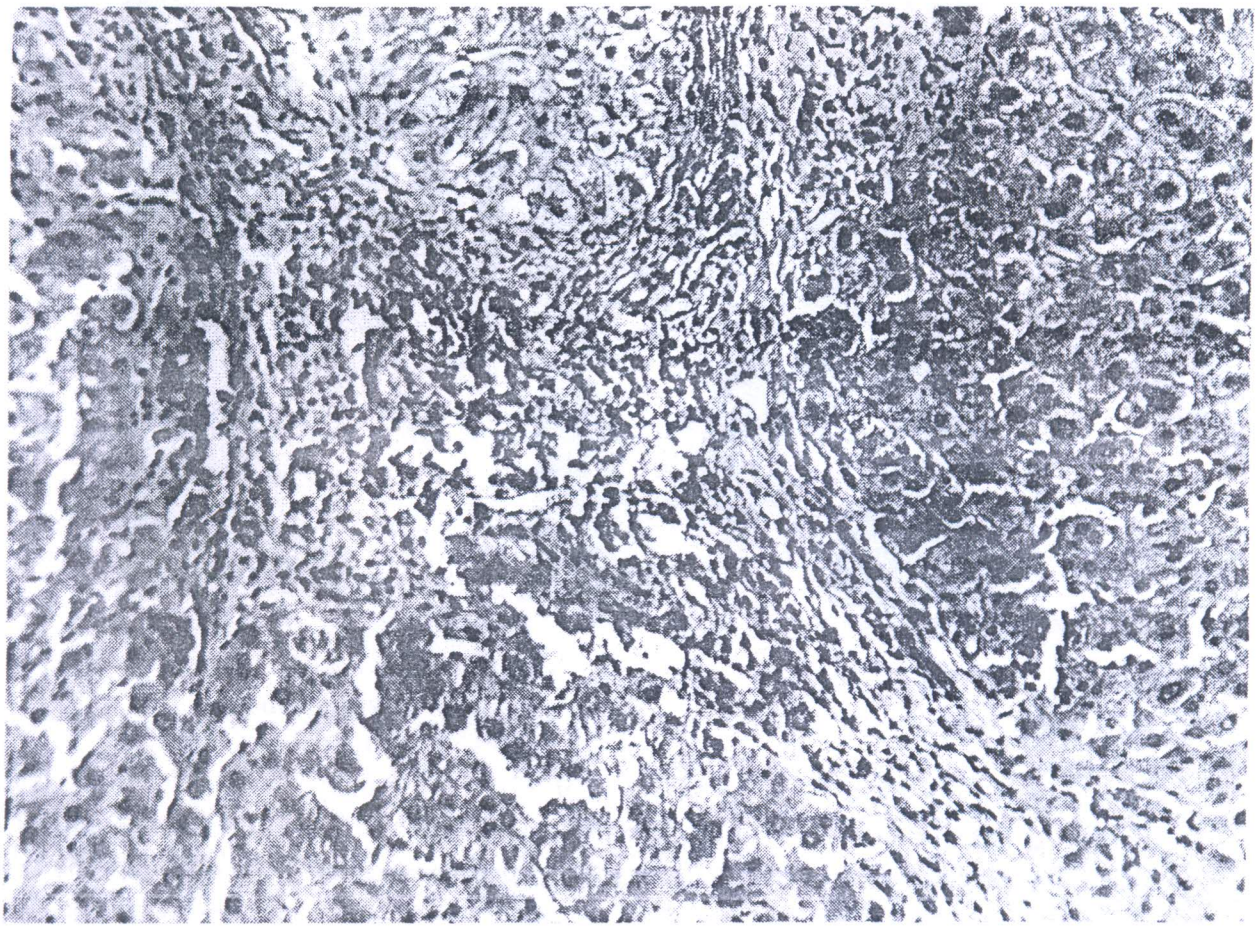


Figure 2. Severe fibrosis of liver with expanded portal zone containing ' ash of vessels, noncirrhotic portal fibrosis, in a patient of chronic arsenic toxicity.

Except for diminished hemoglobin value, no other hematological abnormality was detected in any of the cases. Haemoglobin value was low in 74 out of 156 cases studied.[2] Urine reports and levels of blood sugar, urea and creatinine values were found to be within normal limits. No abnormality in the ECG nor any evidence of renal, cardiovascular and cerebrovascular disease was found in any of the cases studied.

The arsenic levels in hair and nails of the patients were found to be 16.29 ± 3.75 and 42.72 ± 5.92 mg/kg (control values 0.15 ± 0.35 and 0.34 ± 0.24 mg/kg) ($p < 0.001$, $p < 0.001$) respectively. There was no correlation between the quantity of arsenic taken through water and the level of arsenic in hair, and nails.

Discussion

Though the cutaneous manifestations like pigmentation and keratosis, characteristic of chronic arsenic toxicity were quite obvious in people drinking arsenic contaminated water in West Bengal, the patients showed clinical features which were often varied and severe. Few of the affected people reported to city hospitals

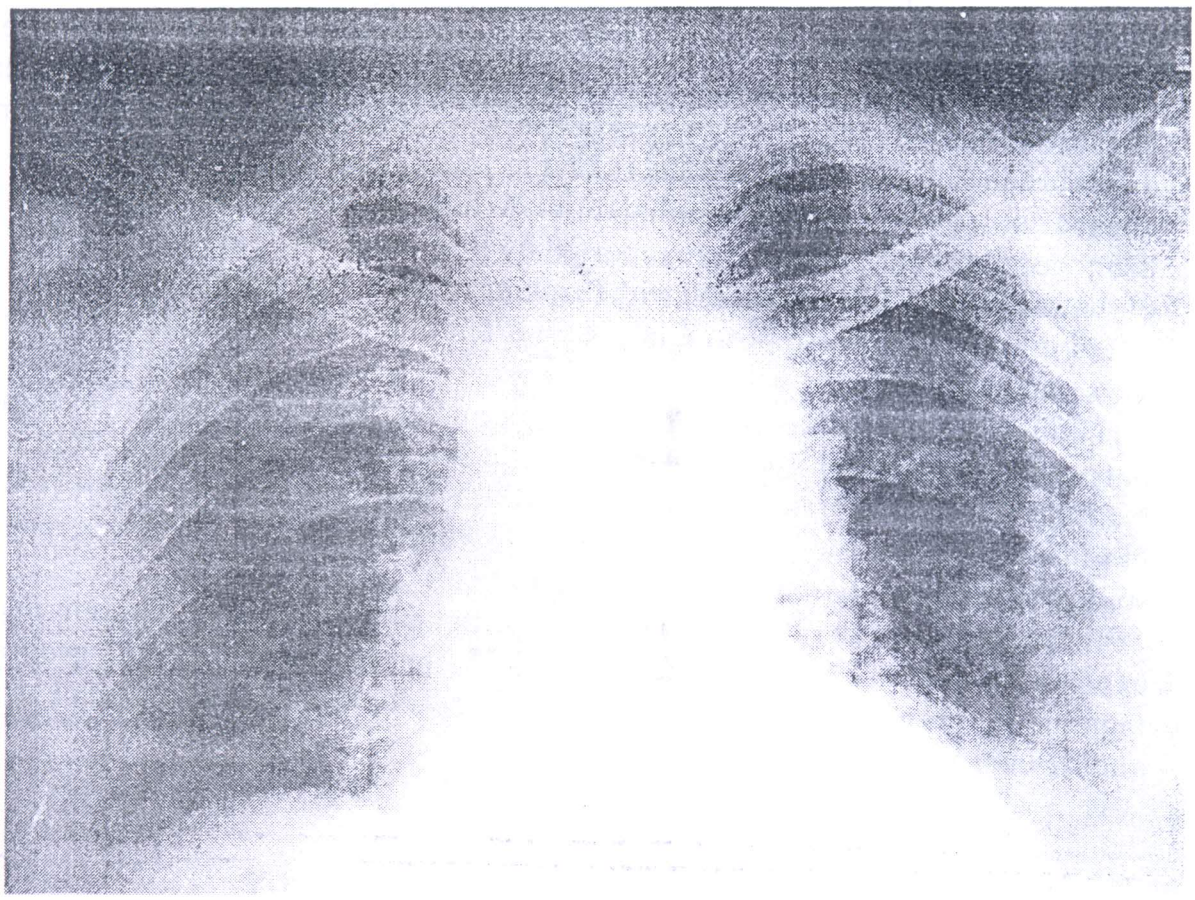


Figure 3. Chest X-ray showing reticulo nodular shadow in both lungs suggesting interstitial lung disease in a patient of arsenicosis.

for their treatment as most of them live in distant rural areas and belonged to low socio-economic class.

Clinical study in West Bengal brought to the notice that significant number of people suffering from chronic arsenic toxicity report to the physician for their complaints of severe weakness, respiratory symptoms, dyspepsia and numbness and weakness of the limbs. Further some people present with features of solid edema of the legs and/or hands, the cause of which is not known.

The high incidence of liver involvement as observed in patients with chronic arsenic toxicity in West Bengal have not been reported previously. Although some reports of liver damage caused by chronic arsenic toxicity were available in the literature earlier,[5,6] few reports emphasized the lesion to be non-cirrhotic. Report of several cases from Europe and our previous published data[4,7] highlight that non-cirrhotic portal hypertension do occur in chronic arsenic toxicity. It was interesting to observe hepatomegaly occurring in a very high percentage (76.6%) of cases of chronic arsenic toxicity. Further NCPF (Non cirrhotic portal fibrosis) on liver histology was found in most of the cases (91.3%) in whom liver biopsy could be done. However, the LFT did not show gross abnormality in most of the patients. Though incidence of NCPF was found to be high among patients having liver enlargement, portal hypertension occurred in smaller number of cases (33.3%).

The high incidence (62%) of respiratory disease among the patients with chronic arsenic toxicity caused by drinking arsenic contaminated water needs special attention. Lung function tests carried out on a small sample of patients showed occurrence of interstitial lung disease with or without airway obstruction. Only two reports are available in the literature on effects of the respiratory system due to exposure of arsenic via routes other than inhalation. A high frequency of chronic cough and bronchopulmonary disease were reported by Borgono et al.[8] among 180 inhabitants of Antafagosta, Chile associated with drinking of arsenic contaminated water. Diffuse interstitial fibrosis was reported in post-mortem reports of 2 out of 5 children from the same area.[6]

Though peripheral vascular disease has been described from Taiwan and Chile[9,10] only small number (1.2%) of cases showed such manifestations in West Bengal. Neuropathy characterized by abnormal EMG and hearing loss as observed by us have also been reported by other workers[11] while diminished NCV was reported in studies from Argentian, Chile and Taiwan.[12]

It appears from the clinical study in West Bengal that there is variation in clinical expression of chronic arsenic toxicity among people from different geographical regions of the world. Further there was no correlation with the arsenic exposure and arsenic level in hair, nail or liver.

B. EPIDEMIOLOGICAL STUDY

To determine the prevalence of the various health effects associated with arsenic, a cross-sectional study was conducted in one of the most affected districts of West Bengal, the South 24 Parganas[13,14] (Fig. 4). This district was a suitable location for this survey because of the heterogeneity in exposure which enabled the investigators to collect exposure response data. The drinking water arsenic levels in this district ranged from nondetectable to 3.4 mg/L.

Methodology

Study Area and Population

Two particular areas within this district were targeted for the survey. The first area was selected because high levels of arsenic were detected in some of the shallow tube wells as determined in a prior study.[4,15] The second area included the remaining part of the district where people also used shallow tube well water for drinking purposes. No survey was carried out by anybody earlier in this area and no reports of elevated arsenic levels were available before the survey. The two areas combined contain a total population of 150,457. A total of 7818 individuals participated in the drinking water study. Water arsenic levels were obtained from 7683 (4093 females and 3590 males) who constitute the study subjects. Ethical clearance was obtained for carrying on human studies from the institutional ethical committee.

Figure 4. Map of West Bengal (India) showing different arsenic-affected districts. Epidemiological study was done in 24 Parganas (South) (shaded area).

Interview and Clinical Examination

Each participant was asked questions about their various symptoms, socio-economic status, their dietary habit, addiction, past history of major illness, and history of parasitic infestation. A thorough clinical examination of each participant was carried out taking special care to detect skin pigmentation and keratosis, enlargement of liver, lung signs and neuropathy. Specific symptoms like weakness, pain abdomen or nausea (suggesting affection of alimentary system) tingling and numbness of the limbs (paresthesia, suggestive of affection of nervous system) were also recorded.

Persons who had liver enlargement were further enquired regarding any past history of jaundice, parasite expulsion, history of taking alcohol or other hepato-toxic drug. In regard to respiratory system, if the participant did not volunteer any information concerning the presence of respiratory problem, they were then specifically

asked on symptom like whether they had any cough or breathing difficulty. Crepitations were determined by auscultation and were defined as the presence of any chest sounds including rals or rhonchi. Participants were also asked if they smoked currently or in the past.

Blood Sampling

Blood samples from willing participants having hepatomegaly were collected for liver function tests like analysis of serum protein, alanine amino transferase (ALT), and serodiagnostic tests like amoebic serology for Entoamoeba histolytica (by commercially available EIA kit) HBsAg by ELISA and Anti HCV by 3rd generation ELISA kit (Hepanostica, Organon Technica, Belgium).

Water Sampling and Arsenic Measurement

Water samples were collected from private and public tube wells used for drinking and cooking purposes by each recruited household. Arsenic levels were measured by flow-injection hydride generation atomic absorption spectrophotometry.[3]

Statistical Analysis

The estimation of the prevalence of keratosis and hyper pigmentation was stratified by age, and calculated for each sex separately. Tests for trends in proportions were based on the chi-square distribution using the mid-points of each grouping of arsenic water levels.[16] Prevalence of liver disease were stratified by age and calculated for each sex separately. The outcomes analyzed also included participant-reported cough, shortness of breath, and weakness, and the presence of crepitations recorded by the examining physician. To allow for direct comparisons without the distorting effects of age, the prevalence of each outcome was directly standardized to the age distribution of all study participants of the same sex. Each outcome was examined according to arsenic levels in the tubewell drinking water source used by each participant which were categorized according to arsenic concentrations as follows: <50, 50–199, 200–499, 500–799, and >800 µg/L. Tests for trend in proportions using the midpoints of the exposure categories were based on the chi-square distribution. In view of uni-directional a priori hypotheses, one-sided *p*-values are presented for the test of trend.[16]

Results

The result of this epidemiological survey in the district of South 24 Parganas showed that the inhabitants were traditionally dependent on ground water and the source was shallow tube wells, varying in depths from 20 to 100 m, some of which had

Table 2. Incidence of various clinical manifestations of chronic arsenicosis: epidemiology study in 24 Parganas (South) 1995–1996.

Symptoms	As Level < 50 μg/L ($n = 3467$) Percent (n)	As Level ≥ 50 μg/L ($n = 4216$) Percent (n)	p Value
Pigmentation	0.34 (12)	8.82 (372)	<0.001
Keratosis	0.11 (4)	3.64 (154)	<0.001
Hepatomegaly	2.99 (104)	10.21 (431)	<0.001
Weakness	1.37 (48)	4.99 (211)	<0.001
Pain abdomen	31.81 (1103)	27.84 (1174)	NS
Nausea	0.31 (11)	0.74 (31)	<0.02
Lung disease	7.74 (269)	11.68 (493)	<0.001
Neuropathy	2.73 (95)	4.70 (198)	<0.001

been found to be contaminated with arsenic. The tube well water concentration in the villages ranged up to 3.4 mg/L, but 88% of the participants with recorded arsenic-water concentrations were exposed to levels less than 0.5 mg/L. Among 7683 people surveyed (which included combined subjects belonging to intensive and cluster survey), 3467 people drank water containing arsenic less than 0.05 mg/L (maximum permissible limit of As in India) and 4216 people drank water containing high level of arsenic (0.05 to 3.4 mg/L). The clinical presentations of the study population giving the incidence of pigmentation, keratosis, weakness, hepatomegaly, chronic lung disease, dyspepisa and neuropathy among both the groups were given in Table 2. Except dyspepisa, the incidence of other features were found to be significantly higher in the As exposed group compared to control population (drinking water ≤ 0.05 mg/L).

Tube Well Water Concentration

Age and sex distribution of the population studied with various dose of arsenic exposure is given in Table 3. Pigmentation (8.82%) and keratoses (3.64%) were the most specific diagnostic parameters of chronic arsenicosis, as none of the people who were drinking water having arsenic level less than 10 μg/L had these features. Keratosis prevalence was examined by arsenic water levels. Of the 4093 female participants, 48 had keratotic skin lesions. A clear relationship was apparent between water levels of arsenic and the prevalence of keratoses (Fig. 5). The test for trend yielded a p value less than 0.001. Similar findings were found for males and for hyper pigmentation in both males and females (Fig. 5). The age adjusted prevalence of weakness was also found to be increased with increasing arsenic water concentration in both sexes ($p < 0.0001$ in both sexes).

Table 3. Age, sex, and arsenic water level (μg/L) distribution of the study population.

	Arsenic Level (μg/L)								
Age Group	<50	50–99	100–149	150–199	200–349	350–499	500–799	≥800	Total
Females									
≤9	194	31	53	23	84	50	75	26	536
10–19	400	74	58	54	117	57	65	26	851
20–29	577	102	99	74	135	63	83	24	1157
30–39	308	79	48	46	79	40	44	15	659
40–49	175	33	23	27	36	21	28	10	353
50–59	157	38	23	18	27	18	30	11	322
≥60	97	29	9	17	27	20	10	6	215
All ages	1908	386	313	259	505	269	335	118	4093
Males									
≤9	220	64	65	27	77	51	81	28	613
10–19	330	73	49	56	96	51	64	29	748
20–29	356	79	56	52	79	43	59	25	749
30–39	246	63	38	40	75	44	53	18	577
40–49	160	43	29	24	53	22	25	12	368
50–59	121	34	20	21	27	16	15	6	265
≥60	126	34	20	21	27	16	15	6	265
All ages	1559	385	274	235	442	245	320	129	3590

Findings Among Those With Low Body Weights

Of the 2320 females and 2132 males with known body weights, 690 (30%) and 808 (38%) respectively were below the standard weight by 20% or more. Compared to those with adequate nutrition, subjects 20% or more below the standard weight had a higher age-adjusted prevalence of keratosis. The overall Standarised Morbidity Ratio (SMR) for keratosis was 2.1 for females [95% confidence interval: 0.8–4.6, $p = 0.07$] indicating that the age-adjusted keratosis prevalence among females with potentialy poor nutrition was approximately twice that of females considered to have adequate nutrition. The overall SMR for males was 1.5 [95% CI: 0.9–2.4, $p = 0.08$]. The combined SMR for both sexes was 1.6 [95% CI: 1.0–2.4, $p = 0.02$].

Arsenic and Liver

It can be seen from Table 2 that enlargement of liver was found in much higher number of people drinking As contaminated water compared to control population (As in drinking water < 0.05 mg/L). History of chronic alcohol intake, past history of jaundice and round worm infection were found among 5 (4.8%), 26 (25%) and 29 (27.8%) participants in the control population while in 19 (4.4%), 55 (12.76%) and 132 (30.62%) subjects in the As exposed group respectively with hepatomegaly. Blood could be tested for viral markers among 26 people belonging to the low exposure

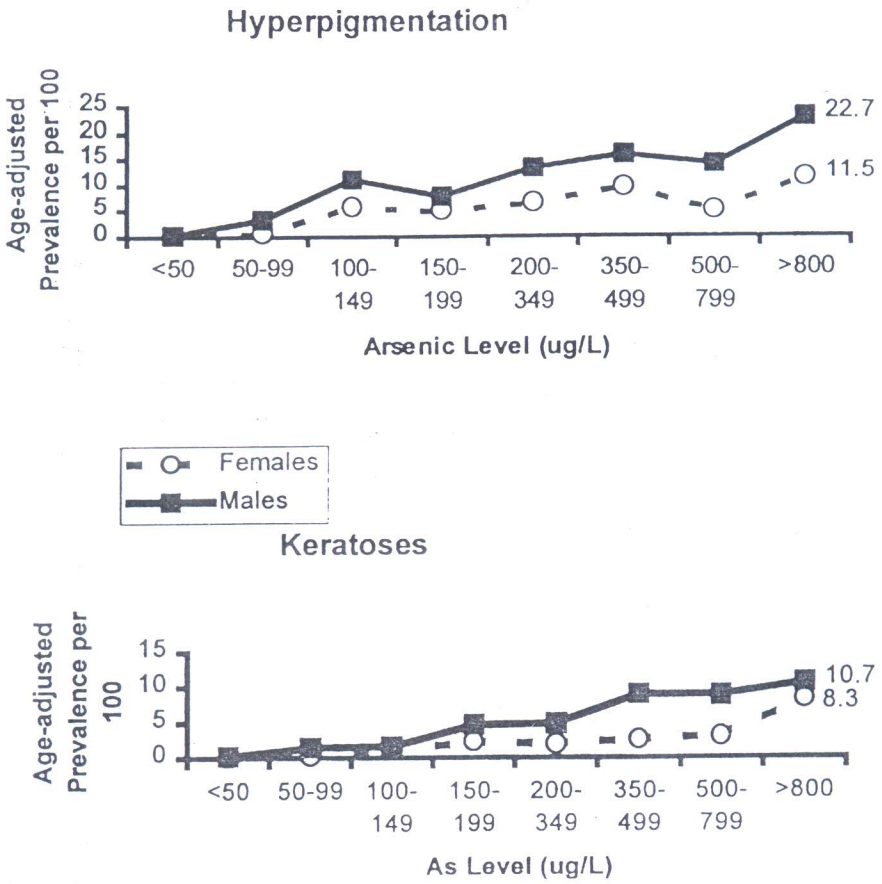


Figure 5. Prevalence of keratosis and hyperpigmentation per 100 for males and females in relation to arsenic exposure in West Bengal. Test for each sex: $p < 0.001$.

group and 143 people to high exposure group. HBsAg was found to be positive in 2 (7.69%) in the former group and 7 (4.82%) in the later group. Anti HCV was negative in all cases belonging to both the groups. Further, anti amoebic anti body titre was found to be high (> 1:125) in the blood of 6 (26.08%) out of 23 participants of the former group and 25 (25.25%) out of 99 participants of the later group. Thus the significantly high incidence of hepatomegaly observed in the As exposed group compared to control population could not be incremented to any of the common etiological factors associated with hepatomegaly in the tropics. Of the various parameters of liver function tests, serum albumin, globulin and ALT levels could be done among 124 people, drinking high As in water (>0.05), having hepatomegaly without any known etiological factor (i.e., history of jaundice, HBsAg and HCV sero positivity and elevated titre of amoebic serology). Abnormal serum albumin level (<3.0 g/dL) was found in 4 cases (3.22%) and globulin (>3.5 g/dL) was found in 17 cases (13.71%) respectively. Elevation of serum ALT (>40 U/L) was found in 27 cases (21.77%).

Prevalence of hepatomegaly corresponding to various As dose exposure among male and females are plotted in Fig. 6. The incidence of hepatomegaly was found to have a linear relationship proportionate to increasing exposure of As in drinking water in both the sexes ($p < 0.001$). The prevalence of hepatomegaly among females was 3.46% in the lower exposure category (<50 µg/L) while its incidence was 17.83% in the highest exposure category (≥800 µg/L). A stronger trend

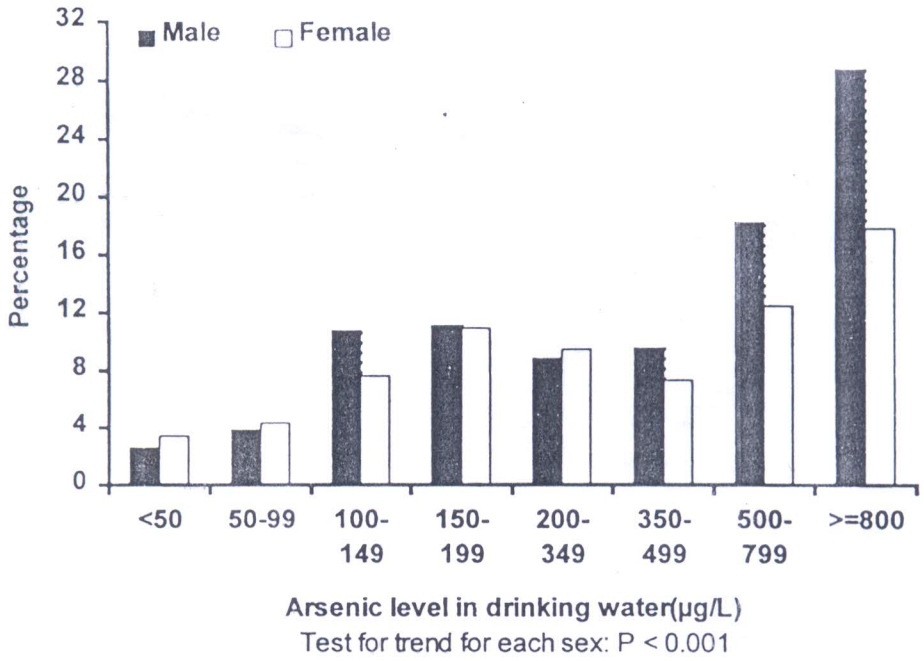


Figure 6. Prevalence of liver enlargement per 100 for males and females in relation to arsenic exposure in West Bengal.

appeared in males, the prevalence increased from 2.62% in the lowest category to 28.81% in the highest exposure category. The prevalence was greater among males than females.

Arsenic and Lung

Results of pulmonary effects manifested by cough, crepitation and shortness of breath among non smokers were analyzed excluding 819 smokers because of their small numbers and potential confounding. Prevalence of cough and crepitation are shown in the Figs. 7 and 8. The overall prevalence in females for each respiratory out come was close to 2.5 per 100. Clear trends of increasing prevalence by arsenic water concentration was seen for cough ($p < 0.0001$) and crepitation ($p = 0.002$). Among males, the overall age adjusted prevalence of cough (5.2 per 100) and crepitation (4.4 per 100) were nearly twice as high as among females but once again there were trends of increasing prevalence by water arsenic concentration ($p = 0.001$ and 0.04 respectively).

Discussion

This is the first population study assessing water levels of arsenic and skin lesions in India in a structured population survey. Clear exposure-response relationships were found with the prevalence of skin effects. The steepest exposure-

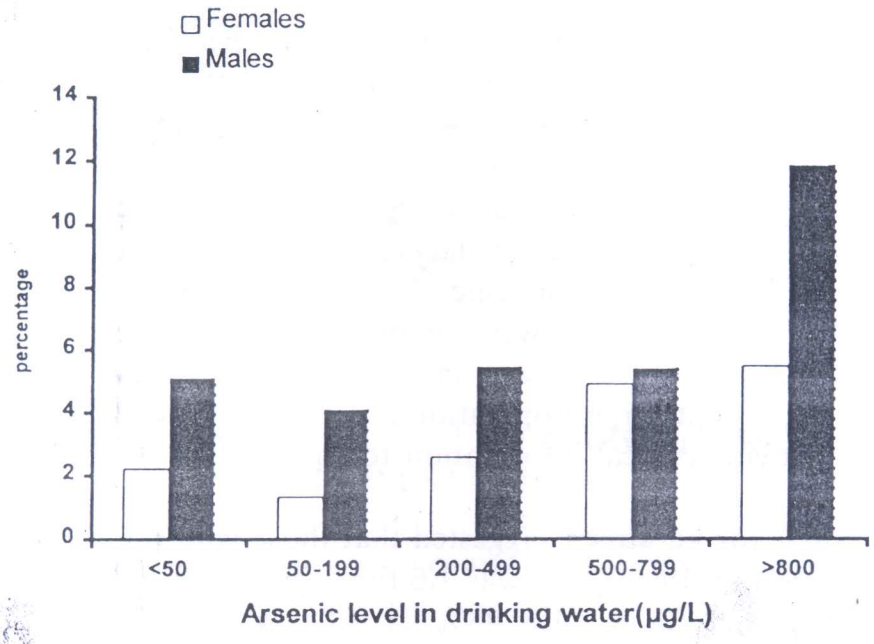


Figure 7. Prevalence of cough per 100 for males and females in relation to arsenic exposure among nonsmokers.

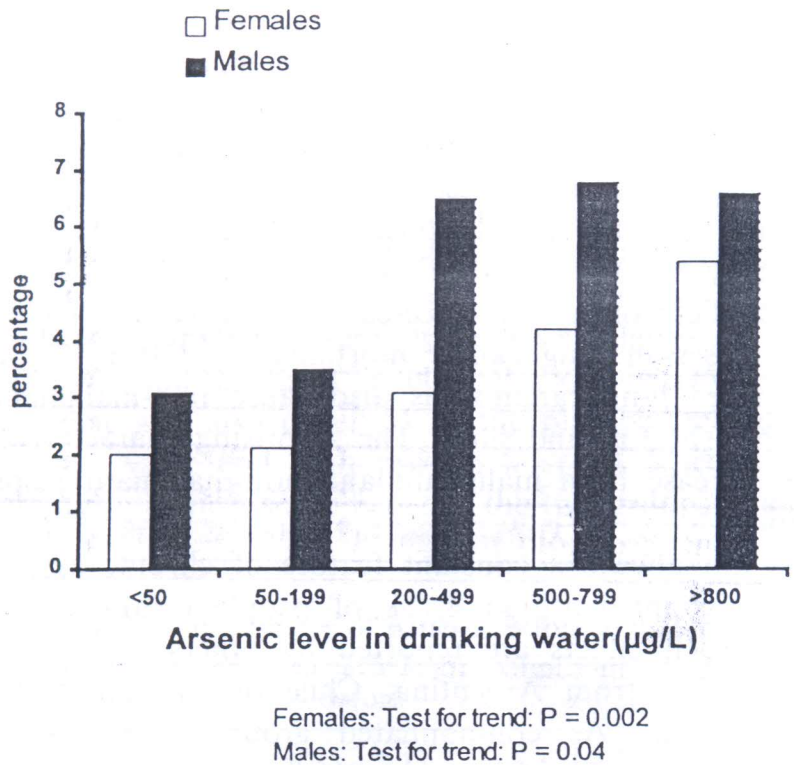


Figure 8. Prevalence of crepitation per 100 in relation to arsenic exposure among nonsmokers.

response relationships were found for males (Fig. 5), this finding is not explained by males having a greater water consumption because this pattern was also apparent using the identical categorization of dose per body weight for both sexes. The most striking finding was that 144 cases with these skin lesions were found among those whose drinking water contained less than 200 μg/L of arsenic. Studies conducted in other countries have also investigated the prevalence of hyper pigmentation and keratoses in regions with elevated arsenic levels in drinking water: however, they either lacked individual exposure data or had small numbers. For instance, arsenic levels in Taiwan were reported in village.[9,10,17] Mean arsenic levels were reported for an entire affected village in Mexico[18] and China,[19] and by towns in Chile.[8] Thus, a major strength of this study is that it is the first large population-based study with individual exposure data, which can provide critical information to characterize the exposure response relationship.

The overall SMR for keratoses suggested that those with poor nutritional status had an age-adjusted prevalence that was 1.6 times greater than those considered to be adequately nourished [SMR = 1.6, 95% CI: 1.0–2.4, $p = 0.02$].

The high incidence of hepatomegaly among As exposed population compared to control group appear to be As related as there was no preponderance of any of the etiological factors for hepatomegaly in the tropics (e.g., history of alcohol intake, jaundice, round worm infestation, HBV, HCV and Amoebic seropositivity)[20] in any of the two groups compared. Further, the prevalence of hepatomegaly was found to have a linear relationship proportionate to increasing exposure of As in drinking water in both sexes ($p < 0.001$; Fig. 6).

This study further provides evidence that ingestion of inorganic arsenic in drinking water results in pulmonary effects manifested by cough, and crepitations in the lungs. In a study of 1774 cases of chronic arsenicosis patients living in 627 villages of Inner Mongolia Autonomous Region of China drinking As contaminated drinking water (As level 0.05–1.82 mg/L), 22.63% of cases showed respiratory system involvement.[21] Although information about the relationship between ingested arsenic and non-malignant respiratory effects has so far only been reported from Chile and now India, and China, studies from arsenic-affected regions in Taiwan, Chile and Argentina show marked increases in lung cancer mortality.[22–26] It is of interest to note that many established lung carcinogens also cause non-malignant lung disease including smoking, asbestos, and silica. The surprising characteristic of arsenic is that it seems to increase both malignant and non-malignant respiratory disease following ingestion.

Neuropathy is not always a constant feature of chronic arsenicosis. Though we have observed its incidence in 4.7% of people drinking As contaminated water and similar such effects are reported by others,[11,27–29] such effects are not reported in studies from Argentina, Chile or Taiwan.[12] Investigation of 530 individuals drinking As contaminated ground water (0.95–2.3 mg/L) in large areas of Inner Mongolila, China showed evidences of peripheral neuritis in 27% of cases and central nevous system dysfunction (abnormal EEG) in 40% of cases.[28]

Interestingly, weakness was found to increase dramatically with increase in As exposure through water in those with skin lesions. The reason why people exposed to high arsenic levels reported feeling weak is not clear. While arsenic can cause peripheral neuropathy, it is not known to cause central nervous system effects that could explain general feelings of weakness. None of our cases did have any evidence of peripheral vascular disease as has been reported in people in Taiwan and Chile.[8,30] However we noticed 3 cases of peripheral vascular disease among 248 cases of our hospital based study where severe cases from the districts reported for their treatment (Vide supra). It appears that the incidence of peripheral vascular disease in West Bengal is quite low.

C. STUDY ON TREATMENT OF CHRONIC AS TOXICITY IN WEST BENGAL

As no effective therapy for chronic arsenic toxicity is known, evaluation of effective therapy for chronic arsenicosis was done by the research group. Chelation therapy for removal of As from body is considered specific for amelioration of symptoms of As toxicity and prevention of its sequelae including cancer.

Chelating Agents

Study with DMSA[31]

Twenty one consecutive patients of chronic arsenicosis were randomized into two groups: 11 patients (10 males, age 25.5 ± 8 yrs) received DMSA (Dimercapto-Succinic Acid) (1400 mg/d in the first week and 1050 mg/d during next two weeks); the same being repeated after 3 weeks period without the drug. The other 10 patients (all male age 32.2 ± 9.9 yrs) were given placebo capsules in the same schedule. The clinical features were evaluated by an objective scoring system before and after treatment. Routine investigations including liver function tests, arsenic level in urine, and skin biopsy evaluation were also made similarly.

Though there was improvement in clinical score in DMSA treated patients, similar improvement was also observed in the placebo treated group who were given only As free water and high protein hospital based diet. There was no statistical difference in clinical score between the two groups both at the beginning

Table 4. Clinical scores of patients before and after therapy.

	Before	After	p Value
DMSA ($n=11$)	9.33 ± 3.33	6.2 ± 2.11	0.017
Control ($n=10$)	10.6 ± 3.20	6.7 ± 1.70	0.003

One way ANOVA.

Table 5. Clinical score of patients before and after therapy.

Clinical Features	Drugs	Before	After	*p* Value
Pigmentation	DMPS	1.45 ± 0.52	0.90 ± 0.54	0.02
	PLACEBO	1.60 ± 0.84	1.10 ± 0.87	0.20
Keratosis	DMPS	1.54 ± 0.68	1.09 ± 0.70	0.14
	PLACEBO	1.40 ± 0.96	1.11 ± 0.87	0.47
Weakness	DMPS	0.91 ± 0.30	0.00 ± 0.00	0.00000031
	PLACEBO	0.80 ± 0.42	0.40 ± 0.52	0.07
Hepatomegaly	DMPS	0.82 ± 0.40	0.45 ± 0.52	0.08
	PLACEBO	0.70 ± 0.67	0.50 ± 0.53	0.46
Neuropathy	DMPS	0.27 ± 0.46	0.09 ± 0.30	0.29
	PLACEBO	0.50 ± 0.70	0.40 ± 0.51	0.72
Lung disease	DMPS	1.82 ± 1.33	0.36 ± 0.80	0.005
	PLACEBO	1.50 ± 1.43	1.10 ± 0.87	0.46
Total scoring	DMPS	8.90 ± 2.84	3.27 ± 1.73	0.00017
	PLACEBO	8.50 ± 1.96	5.40 ± 2.12	0.003

and at the end of treatment. Similarly no difference of other parameters investigated were found among the DMSA treated and control group (Table 4). The study demonstrated that DMSA is not effective in causing any clinical or biochemical benefit and histopathological improvement of skin lesion in patients of chronic arsenicosis.

Study with DMPS[32]

2,3-Dimercapto-1-propanesulfonate (DMPS), a chelating agent, has recently been found to increase excretion of arsenic (As) in urine several folds above prechelation levels. However, therapeutic efficacy of DMPS in the management of chronic arsenic toxicity has not yet been properly evaluated. Clincial use of DMPS in such patients were studied at SSKM Hospital.

Twenty one consecutive patients with chronic arsenic exposure were individually randomized into two groups; 11 patients (9 males, 2 females, age 30.63 ± 11.4 years) received DMPS 100 mg capsules four times a day for one week and repeated on 3rd, 5th, and 7th week with no drug during the intervening period. The 10 patients (5 males and 5 females, age 34.4 ± 14.41 years) were given placebo capsules (resembling DMPS) in the same schedule. The patients were blinded about the nature of treatment given.

Therapy with DMPS caused significant improvement of clinical condition of chronic arsencosis patients as evident by significant reduction of total clinical scores from 8.90 ± 2.84 to 3.27 ± 1.73; $p < 0.0001$. Clinical score of patients before and after therapy are given in Table 5. Total urinary excretion of DMPS treated cases was found to increase significantly following drug therapy, while no such increase was noticed in placebo treated cases. This is the first time we demonstrated that a chelating agent

(DMPS) treatment caused significant improvement of clinical symptoms of patients suffering from chronic arsenic toxicity. Increased urinary excretion of arsenic during the period of therapy is the possible cause of this improvement. However, further study with this drug on a large number of cases treated for a prolonged period need to be carried out before recommending this drug for regular use in the treatment of arsenicosis.

Postscript: Treatment of Chronic Arsenic Toxicity

People should be advised to stop drinking As contaminated water or exposure to As from any other source. Follow up study carried out in West Bengal showed that drinking of As free water did cause improvement of skin manifestations, weakness, anaemia and neuropathy in a significant number of cases.[33] Supportive treatment could help in reducing many symptoms of the patients. Treatment in hospital with good nutritious diet has been found to reduce symptom score in a subset of placebo treated patients in West Bengal during the course of DMSA trial.[31] High protein containing diet, possibly helps in clearance of inorganic As (more toxic) by increased methylation. Thus people should be urged to take food containing proteins in good quantity either from animal source or if unable, from vegetable sources like pulses, soybeans, wheat etc.

Retinoids and antioxidant: Etretinate and other retinoids have been reported to have anti keratinizing effect and may have beneficial role for chemo prevention of cancer. However high dose of rationol have adverse effect, including teratogenesis and liver toxicity. Hence prospective randomized control trial with proper surveillance is needed to evaluate whether its beneficial effect overshadows the side effect.

The various clinical manifestations should be treated symptomatically. Chronic bronchitis with or without obstruction are the common causes of morbidity in many cases of chronic As toxicity. It is extremely important that bronchial irritation should be reduced to a minimum. The patient who smokes should be urged to stop smoking completely and permanently. Dusty and smoke laden atmospheres should be avoided. Respiratory infection should be treated promptly because it aggravates breathlessness. Purulent sputum may be treated with oral oxytetracycline or ampicillin in a dose of 250–500 mg 4 times a day or Co-trimoxazole 960 mg twice daily. A 5–10 day course of treatment is usually effective and sputum becomes mucoid. Bronchodilators are much less effective in chronic bronchitis than in bronchial asthma, but should be given to all patients with reversible airflow obstruction. Regular treatment with an inhaled beta$_2$-adrenoreceptor agoinst (Salbutamal 200 mcg or terbutaline 500 mcg, 4–6 hourly) may be sufficient in patients with mild to moderate airway obstruction disease. The anticholinergic bronchodilator drug ipratropium bromide in a dose of 36–72 mcg 6 hourly may be added in patients with more severe air flow obstruction. Theophyllin therapy often has little measurable effect on the airway obstruction associated with chronic bronchitis, but it will improve quality of life in some patients. Treatment option for interstitial lung disease is limited. Dyspeptic symptoms associated with chronic arsenicosis could be easily managed by

use of H_2 receptor blockers with/without prokinetic drugs. Though non cirrhotic portal fibrosis occurs in some of these patients, the incidence of portal hypertension is quite low. When varices are detected by endoscopy, prophylactic therapy by beta-blockers may be of help. Sclerotherapy or banding may be needed for the management of variceal haemohage. Peripheral vascular disease associated with gangrene are difficult to treat because of severe pain. Pharmacological agents like pentoxyphyllin or calcium channel blockers are found to have limited effect. Most of these patients need surgical amputation. Symptoms of peripheral neuropathy improve in some on stoppage of drinking As contaminated water. Tricyclic antidepressents such as amitryptiline may have utility in relieving painful dysthesias of arsenical peripheral neuropathy.[34] Skin thickening of the sole and palm can be treated by local application of keratolytic ointment (Containing 5% salicylic acid).[35,36]

As most of the case fatality due to chronic arsenic toxicity occurs due to cancer of skin, urinary bladder and lung, cancer surveillance and early detection of these cancers need to be ensured. Surgical resection of skin and bladder caner is curative if detected early.

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