Arsenicosis:
A Global Issue

Mir Misbahuddin
MBBS, PhD, Professor

SciencePG
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Preface

1. Why did I Decide to Write this Book?

I considered deeply who will be the reader before deciding to write this book. When you look at the Indian history of educational system, guardian sent his child to the teacher's house (Gurugriho) for learning. Subsequently teacher shifted his class from the house to under a tree when the number of students increased. Later on, teaching was limited to textbook and brick-based face to face teaching at classroom. At present teaching contents are available in internet.

Arsenic contamination has changed our concept of safe drinking water. We failed to motivate our people, politicians and beurocrates to understand the risk assessment process that other risks to life and livelihood are as grave as arsenic. A lot of information is available about arsenic and arsenicosis in internet. Reader has less time to read those and sometime confused which are authentic.

2. Who is the Reader?

Doctor working in the arsenic endemic area will be the reader of this book.

3. How I became a Toxicologist?

I joined in my present working place as Associate Professor in 1993. The

research activities in our department were mainly focused on the therapeutic effects of spirulina, a blue-green algae. High concentration of arsenic in the drinking water as well as case of arsenicosis was first diagnosed in Bangladesh in 1993. Two to three years were required for official recognition of this disease by the Government of Bangladesh. In 1997, one of our MPhil students showed interest to examine the curative effect of spirulina in arsenicosis as a part of his thesis work. At that time we had no facility for the estimation of arsenic in water or urine. We, then, started to use the qualitative method (Gutzeit's test) for the presence of arsenic. Then we conducted an open trial on a few cases of arsenicosis with spirulina, which is available in our drug store as alternative medicine. Therefore, we purchased spirulina powder and then provided to patients as a part of treatment because there was no specfic treatment of arsenicosis. Surprising results were obtained when we saw the clinical improvement after 4 months of treatment. That study was not well designed and we did not estimate the amount of arsenic in hair or nail. Only urine of the patient was examined for the presence of arsenic in order to confirm the diagnosis. Then I thought how spirulina relieved arsenicosis. I placed some spirulina powder in an ordinary syringe (5 mL) and placed vertically like a column chromatography. I poured some amount of arsenic contaminated water at the top of spirulina powder and then collected water sample in a test tube placed at the bottom. The water sample was then tested for total arsenic level. Arsenic was not found when it passed through spirulina. Then my idea was shifted from spirulina to water hyacinth. As arsenic is present in underground water in Bangladesh, but not in surface water like pond or river. Pond contains a lot of water hyacinth. Like spirulina, water hyacinth may have an important role in removing arsenic from pond's water. I collected some water hyacinth and placed in a bucket containing arsenic contaminated water. Again I surprized to see that water hyacinth removed arsenic from water within a few hours.

When I go through the published articles on arsenic, I found that Bangladesh is

severely affected by chronic poisoning with high concentration of arsenic. Most of the research works were done on epidemiology and mitigation. Only a few papers were on the treatment of arsenicosis.

Then I decided to start research to find out a drug that will be effective for the treatment of arsenicosis. I changed my laboratory setup that is gradually shifted from the Gutzeit's method to other methods using spectrophotometer, atomic absorption spectrometer (AAS) and atomic fluorescence spectroscopy (AFS).

4. What Initiates me to Write this Book?

One day I received an email from the Science Publishing Group to wtire a book. Then I decided to write a book on arsenicosis.

5. Answers of Many Questions

I wanted to solve a number of questions that had been raised in a scientific saminar on "Arsenic: Health effects, mechanism of action and research issue" held in September, 1997 at Maryland, USA.

6. Previous Experiences

I wrote two arsenic related books. These previuos experiences helped me in writing this book.

7. Authanticity

A lot of information is given in this book. Only the future will tell what percentage of the information in this book is correct.

I must thank the publisher to publish a book on arsenicosis by an author of a country where arsenic-related health problem is the top among the countries of the world.

M. M.
Division of Arsenic Research
Department of Pharmacology
Faculty of Basic Science and Paraclinical Science
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka, Bangladesh.

March 2015

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Chapter

1

〖Introduction〗

"For many people in Bangladesh it can sometimes literally be a choice between death by arsenic poisoning and death by diarrhea."

Timothy Claydon, Country Representative of Water Aid

Arsenic (from the Greek word *arsenikon*, meaning "potent") is a metalloid present everywhere (i.e., water, soil and air). It enters into our body when the water we drink, the food we eat and the air we breathe. Even a person comes in contact with soil or water containing arsenic may have arsenic within the body. Some pathological changes only occur when we consume it more than the safe level. This consumption may be acute, previous, intermittent or chronic. There is no scope to discuss in this book about acute consumption. Previous exposure to arsenic is important when we look after the findings of Taiwan (Chen et al., 1962) and Chile (Unicef, 2008). Chronic

consumption of high concentration of arsenic affects any organ of the body. However, there may be no symptom, particularly in skin or failure of correlation between the arsenic consumption and involvement of other organ(s) which may be called preclinical. Most of the people in arsenic endemic area consuming arsenic are in preclinical state. Only a small percentage (?) of people consuming arsenic for a long time show skin manifestations (mostly non-malignant). There may be involvement of internal organs. Arsenic is a class A human carcinogen, which causes an increased risk of cancer usually originating from the skin, lungs, liver, kidneys and urinary bladder.

People in arsenic endemic area consume arsenic unknowingly or knowingly due to its physical characteristics (no odor, no color, and no taste). If we consider the history, the mummified bodies in Chile showed signs of arsenic exposure from as long as 7,000 years ago (Arriaza et al., 2010). Arsenic (Figure 1.1) has been known as a 'silent toxin' since ancient times. It was only two decades ago that it received overwhelming worldwide public attention (Jean et al., 2010).

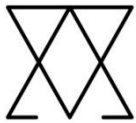


Figure 1.1 *Alchemical symbol of arsenic.*

1.1 Multiple Terminologies

Health problems after chronic consumption of arsenic have more than 10 terminologies. These are chronic arsenic poisoning, chronic arsenic toxicity, arseniasis, arsenism, arsenicism, arsenicalism, hydroarsenicism, HACRE (Spanish word: Hidroarsenisismo Crónico Regional Endémico), arsenicosis, chronic arsenicosis, arsenicosis patient or arsenical dermatosis. It has also local name like "Kai Dam" in Thailand, "Bell Ville" in Argentina and "Blackfoot

disease" in Taiwan. Bell Ville is the name of an area near Córdoba city, Argentina, where cases of arsenicosis were first diagnosed. Blackfoot literally means "black and dry snakes". Some of the terminologies are used for certain period. For example, arsenicalism was used between 1950s and 1990s. The number of terminologies is due to regional variations and time variation.

When you enter the three terminologies 'chronic arsenic poisoning', 'chronic arsenic toxicity' and 'arsenicosis' into the internet www.scholar.google, the results show that chronic arsenic poisoning is the most preferred term whereas chronic arsenic toxicity is the least (Table 1.1). In each case, prevalence, diagnosis, prevention and treatment were added for search.

Table 1.1 *Hits in Google Scholar (up to May 2014).*

Terminology	Prevalence	Diagnosis	Prevention	Treatment
Chronic arsenic poisoning	1280	1670	1470	3060
Arsenicosis	1230	1130	1390	1130
Chronic arsenic toxicity	663	711	739	1450

However, the term "arsenicosis" may be more acceptable. The term "arsenicosis" was first detected in a paper (Journal of Association of Physicians India) in 1976 written by D. V. Datta and M. K. Kaul (Datta & Kaul, 1976). It is difficult to say who first coined this terminology. There is no need to use the word "chronic" when "arsenicosis" is used. Similarly "arsenicosis patient" is not necessary to use. The word "arsenicosis" is self-explanatory. The next option is the "chronic arsenic toxicity". That is, toxicity develops following chronic ingestion of high concentration of arsenic in drinking water.

In scholarly journals, some authors choose the term "keratosis" whereas others use the term "hyperkeratosis". This leads to confusion between keratosis and hyperkeratosis. Keratosis means growth of the keratin layer on the skin or on mucous membrane. Hyperkeratosis is the severe form of keratosis. It is better

to avoid the term “hyperkeratosis”. The term “arsenical keratosis” may be used as because keratosis may develop from other causes. Keratosis in the palm or sole may be more appropriately accepted as “palmar arsenical keratosis” or “plantar arsenical keratosis”.

1.2 Definition

A working group of World Health Organization (WHO) regional office at New Delhi in 2003 defined arsenicosis as a “chronic health condition arising from prolonged ingestion (not less than six months) of arsenic above a safe level, usually manifested by characteristic skin lesions, with or without involvement of internal organs” (Caussy, 2005).

In this definition, emphasis was given on the presence of non-malignant skin manifestations. Therefore, arsenicosis may be better defined as “pathological changes develop in any organ of the body due to chronic or previous consumption of high concentration of arsenic”. The skin, body’s largest organ, is primarily affected. The patient attends the doctor with complain for treatment. Arsenicosis is difficult to diagnose when organ(s) other than skin are affected due to absence of any specific biomarker.

1.3 Types of Arsenicosis

Arsenicosis can be classified into three types based on method of contamination. These are medicinal arsenicosis, occupational arsenicosis, and dietary arsenicosis. Cases of medicinal arsenicosis were reported first, followed by occupational arsenicosis and dietary arsenicosis. When we consider the extent of arsenicosis, only limited numbers of cases were reported as medicinal and occupational arsenicosis. On the other hand, the extent of dietary arsenicosis is

severe. Arsenicosis due to high concentration of arsenic in air (as arsenic trioxide; As_2O_3) is only reported in China.

Initially it was thought that the presence of arsenic in surface and groundwater was due to mining (Sambu & Wilson, 2008). Cases of arsenicosis were detected in Hungary in 1940s. A survey conducted by the Hungarian Public Health in 1982 concluded that the high level of arsenic was due to natural biogeochemical process instead of anthropogenic activities (Csalagovits, 1994).

Medicinal arsenicosis: Arsenic had been used as medicine for at least 2,500 years. Hippocrates (460-377 BC) used orpiment (As_2S_3) and realgar (As_2S_2) as escharotics, a caustic material that burns flesh away. Aristotle (384-322 BC) and Pliny the Elder (23-79 AD) also wrote about the medicinal properties of arsenicals. Galen (130-200 AD) recommended a paste of arsenic sulfide for the treatment of ulcers. Paracelsus (1493-1541) used elemental arsenic extensively (Jolliffe, 1993).

For the last two centuries, it was used by the physicians to treat dermatitis herpetiformis, asthma, syphilis, epilepsy, psoriasis, and amebiasis. Cases of arsenical dermatitis were reported in 1884 (White, 1884). Sir Jonathan Hutchinson, in 1887, first clearly related the development of keratosis and skin cancer to long-term ingestion of arsenic as Fowler's solution (1% potassium arsenite, $KAsO_2$). Fowler's solution was first discovered in 1786 and was also used as medical tonic. In 1912 arsenic was recognized as the best agent in the Pharmacopoeia (Frost, 1977). It is also used in the form of Donovan's solution (AsI_3), and the Asiatic pill (As_2O_3). Asiatic pill was taken with pepper or opium. German physician Paul Ehrlich and Japanese student Sahachiro Hata produced their 606^{th} preparation of an arsenobenzene compound (salvarsan) in 1907. Ehrlich watched on 31 August, 1909, as Hata injected chemical No. 606 into a rabbit with syphilitic ulcers. Subsequently it was used in the treatment of

syphilis. Inorganic arsenic (when arsenic combines with oxygen, sulfur or chloride) is still available in Traditional Chinese Medicine preparations (Espinoza et al., 1996). For example, the Chinese herbal ball named 'An Gong Niu Huang Wan' (in English: Calm the palace pill with cattle gallstone) is used in the treatment of high fever, irritability, restlessness, delirious speech contains high concentration of arsenic (3.21 to 36.6 mg per herbal ball).

When the cases of arsenicosis were identified due to intake of arsenic as medicine, then the prescriptions of arsenic containing medicines were stopped. However, in 2000, arsenic trioxide was approved by Food and Drug Administration (FDA) for the treatment of acute promyelocytic leukemia (FDA, 2000). About 75 percent of acute promyelocytic leukemia patients can be cured with other combination therapies, but those who do not achieve remission or who relapse can be treated with arsenic trioxide.

Occupational arsenicosis: Occupational arsenicosis may be due to a) working in mining, b) use of pesticide or fertilizer, c) sweeping chimney, and d) use of arsenic contaminated paint or timber. Keratosis was observed in female workers in a chemical plant who were exposed to arsanilic acid (0.065 mg/m^3; Chou et al., 2007). Copper arsenite was used as a pigment for making wall paper and paint. Arsine gas exposure was found following ore smelting, electroplating, manufacturing brass, dyeing or gold extraction.

Pesticide: Paris green (copper acetoarsenite) was first used against the potato beetle in the Western USA in 1865 and its use was well established in 1868 (Frear, 1942). Between 1880 and 1900, Paris green was probably the most commonly used insecticide, with London purple (an arsenic compound) a close second (Frear, 1942). Arsenic trioxide was used as insecticide, rat poison, weed killer, sheep dip and hide preservative. Lead arsenate and calcium arsenate were used as insecticide.

The pesticides monosodium methane arsonate (MSMA), disodium methane arsonate (DSMA), calcium acid methane arsonate (CAMA), and cacodylic acid were used as herbicides on cotton and other agricultural crops. All uses of DSMA, CAMA, and cacodylic acid were canceled on September 30, 2009. The use of MSMA was prohibited after December 31, 2013.

Sweeping chimney: In 1775, the English Surgeon Sir Percivall Pott (1714-1788) first reported the case of skin cancer at scrotum among the chimney sweeper (Pott, 1775). In 1820, the English physician John Ayrton Paris (1785-1856) first reported the association between arsenic and the development of cancer as occupational (Blejer & Wagner, 1976). While sweeping the chimney, these patients were exposed to soot that contained sulfur dioxide and arsenic.

Wood preservative: Chromated copper arsenate was introduced as wood preservative by an Indian mining engineer in 1933. Arsenic releases into the soil and raised the concentration of arsenic. Thus, children sickened by contact with playground equipment built from arsenic-treated wood. Similarly, burning arsenic-treated wood can result in elevated arsenic levels in smoke. It is no longer used since 2003.

Dietary arsenicosis: Arsenicosis develops due to intake of high arsenic contaminated drinking and cooking water [as inorganic arsenate (AsO_4^{3-}) or arsenite (AsO_2^-)], and foodstuffs. Arsenical keratoses of the palms and soles were first described by Erasmus Wilson in 1873 (White, 1885). In 1900, about 3,000 people developed arsenicosis in Manchester, England, as a result of drinking beer which had been sweetened with glucose containing arsenic (McNeer, 1934).

As early as in 1809, William Lambe expressed the belief that arsenic in potable

water may be the cause of malignant disease (Eggers, 1931). The contamination of drinking water resources by geogenic arsenic was first described in Argentina in 1913 (Goyenechea, 1917). The river water in some areas of Argentina and Chile is contaminated with high concentration of arsenic. Subsequently it was detected in other countries. In Taiwan the arsenic exposure occurred between 1910s and 1970s due to use of water from artesian well (Hsueh et al., 1995), and the blackfoot disease was first diagnosed in 1954 (Table 1.2). In India, arsenic pollution of groundwater was first discovered in Chandigarh in 1976 by doctors (Datta, 1976)

Table 1.2 *Detection of first case of arsenicosis.*

Country	Year of first detection
Argentina	1917
Taiwan	1954
Mexico	1958
Chile	1962
China	1980
Iran (Kurdistan)	1981
India	1976
Thailand	1987
Mongolia	1990
Bangladesh	1993
Nicaragua	1996
Nepal	2003
Cambodia	2006

after a patient who died of liver disease was found to have high levels of arsenic in all internal organs. The presence of large number of cases of arsenicosis was reported in Kolkata, West Bengal in 1984 (Garai et al., 1984). The first case of arsenicosis due to chronic consumption of drinking water in Bangladesh (Chapai Nawabganj, a district close to the border of West Bengal, India) was diagnosed in 1993. The groundwater of Bangladesh and India (West Bengal) is contaminated

with high concentration of arsenic (Misbahuddin et al., 2011). The amount of arsenic in hand pump tube wells of different sites on an endemic area varies with wide range.

Sea food contains high concentration of organic arsenic (when arsenic combines with hydrogen and carbon). Foodstuffs in arsenic endemic area are contaminated with high concentration of arsenic which is due to contamination of soil by geological or anthropogenic cause. Flood or mining affects the level of arsenic in soil. Irrigation of agricultural land by arsenic contaminated deep tube well water is an important factor of contamination of soil in Bangladesh and India. On the other hand, soil of gardening area near the house is less contaminated with arsenic. All foodstuffs are not equally contaminated with arsenic. The staple food of some countries, for example, rice is contaminated with arsenic.

Arsenicosis due to inhalation of arsenic: When air containing arsenic dusts is breathed in, the majority of the dust particles settle onto the lining of the lungs (Chen et al., 2006). High level of arsenic is present in air of some areas in China. The arsenic concentration in kitchen air following coal burning is 160-760 $\mu g/m^3$ (average: 445 $\mu g/m^3$). Coal can contain very high levels of arsenic, up to 3.5% arsenic by weight. Millions of people around the world burn coal in the household in non-ventilated stoves for cooking, heating the room during winter season, and in some cases for drying food. Arsenic-contaminated coal, when used for these purposes, may cause arsenicosis. This is particularly apparent in some areas in Guizhou Province of China.

Cow dung is found to cause arsenicosis in West Bengal, India (Pal et al., 2007). The cow dung, from cows fed contaminated rice straw, is dried in the sun and used as fuel in domestic ovens. When the cow dung cakes are burnt arsenic is released into the air, which is then inhaled by the people.

Seekh kebab is a popular diet of South East Asian countries where coal is burned to prepare it. The fume produced from coal is inhaled by the cook. The extent of arsenic while preparing seek kebab is not known.

Arsenicosis cases were first documented in patients following chronic administration of Fowler's solution as medicine. Subsequently paints and pesticides were responsible for the development of arsenicosis. These were man-made and the number of cases was reduced after stoppage of usage. Later surface and groundwater were identified for the development of arsenicosis.

1.4 Outline of Sources of Contamination

The presence of high concentration of arsenic in the environment for human consumption is due to geogenic, anthropogenic or biogenic (Figure 1.2).

Geogenic sources of arsenic contamination are geothermal/volcanic activities and weathering of rocks and minerals. Geothermally active zones occur to plate boundaries, in tectonic rift areas and at "hot spots" where mantle-derived plumes ascend. In Taiwan, groundwater from artesian wells completed in black shales, muds and fine sands are contaminated with arsenic. The presence of arsenic in surfaces and groundwater in Latin America is associated with tertiary and quaternary volcanism in the Andes Mountains.

Himalayas has formed the extensive alluvial plain and delta through which the Ganges, Brahmaputra and Meghna rivers flow and which form aquifers in India and Bangladesh. Anthropogenic contamination of arsenic is due to human activities includes mining and processing of ores and manufacturing using arsenic-bearing sulfides. The use of organic arsenic-based pesticides in agriculture causes contamination of groundwater in Mexico, USA and India. Biogenic sources of arsenic contamination include plants, animals and

microorganisms.

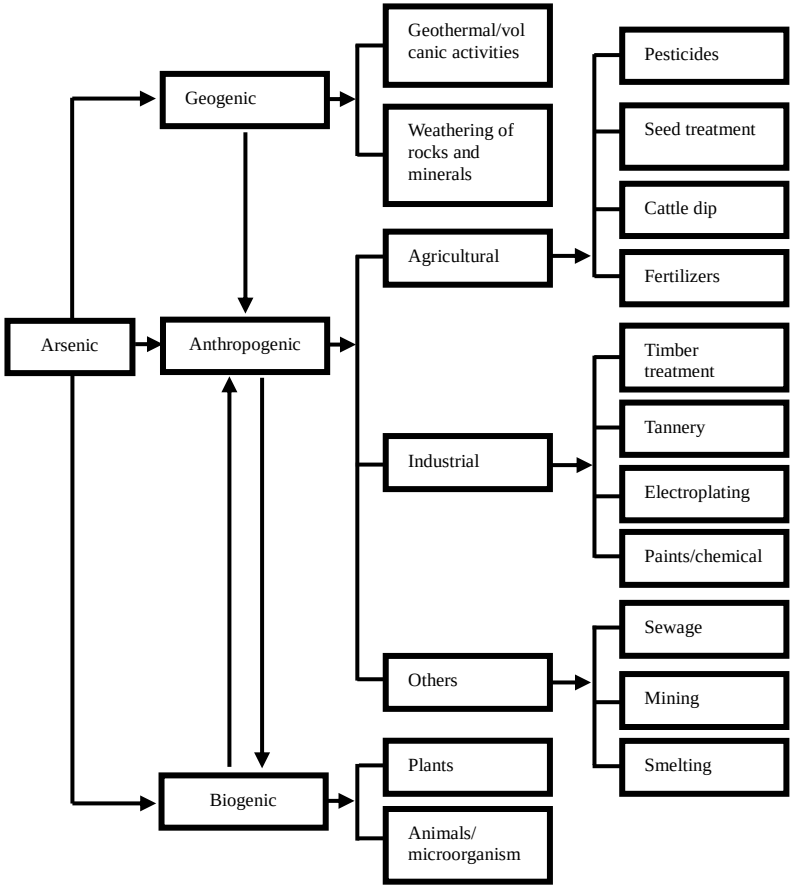


Figure 1.2 *Major sources and routes of arsenic in soil and aquatic ecosystems (Mahimairaja et al., 2005).*

1.5 Safe Level of Arsenic

The concentrations of arsenic vary: nanogram per cubic meter level is present in air, microgram level per liter in water and milligram level per kg in soil (Table 1.3). That is, there are thousand time differences in each level. There is also regional variation. The word ‘safe’, here, means the level of arsenic when

exposed chronically to human body does not produce any adverse effect after a long time. However, in true sense, it is difficult to measure.

Air: The usual level of arsenic in air is 1-3 ng/m^3 in rural area and 20-100 ng/m^3 in urban area in USA. In European regions, it is between 0.2-1.5 ng/m^3 in rural areas, 0.5-3 ng/m^3 in urban areas and no more than 50 ng/m^3 in industrial areas (DG Environment, 2000). In England, the mean concentration is 5.4 ng/m^3, with a declining trend over the period 1957-1974 *(*Salamon, 1978*)*. In Canada, the mean level is 1 ng/m^3 (range 0.5-17 ng/m^3) (Hughes, 1994).

Table 1.3 *Safe level of arsenic.*

Site	Amount of arsenic
Air (rural area, USA)	1-3 ng/m^3
Air (urban area, USA)	20-100 ng/m^3
Soil (USA)	7.2 mg/kg
Water	5, 7, 10, 25, 50 ppb
Food	??
Human	
Blood	<1 ppb
Urine	<100 ppb
Nail	<1 ppm
Hair	<1 ppm

Soil: Arsenic is present in soil at levels ranging from 0.2 to 40 mg/kg. It is rarely more than 10 mg/kg.

Drinking water: The safe level of arsenic in drinking water is still confusing (5, 7, 10, 25 or 50 ppb). WHO in 1958 recommended drinking water standard of 200 ppb which was reset to 50 ppb in 1963 and 10 ppb in 1993.

For American, it is 10 ppb whereas 50 ppb for Bangladeshi (Table 1.4). It is not clear about the discrepancy. Skin manifestations of arsenicosis are found in some Bangladeshi patients where their drinking water levels are below 50 ppb

level. Therefore, 10 ppb may be considered as safe level.

Is it possible to change the safe level of arsenic to 10 ppb where it is 50 ppb? If we look after this case in USA, a developed country, it took about 10 years to implement 10 ppb from 50 ppb. The main problem of implementing 10 ppb in developing countries, like Bangladesh, is the absence of sensitive method for the estimation of arsenic. There may be involvement of other factor(s) including genetic factor.

Table 1.4 *Country-wise safe level of arsenic in drinking and cooking water.*

Safe level of arsenic in water	Country
5 ppb	USA (State of New Jersey)
7 ppb	Australia
10 ppb	Alaska, Argentina, Austria, Bolivia, Brazil, Chile, Colombia, Costa Rica, El Salvador, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Itali, Japan, New Zealand, Nicaragua, Panama, Russia, Spain, Sweden, UK, USA, Vietnam
25 ppb	Canada, Mexico
50 ppb	Bangladesh, China, Cambodia, India, Laos, Myanmar, Nepal, Pakistan

Food: Bangladesh or India has not yet set standards for arsenic in foods, but the Chinese government in 2005 fixed a limit of 0.15 mg/kg inorganic arsenic in rice. WHO has established a provisional Maximum Tolerable Daily Intake (MTDI) of 2.1 μg/kg body weight inorganic arsenic that should include exposure from food and water.

With the exception of some kinds of seafood, most foods contain low levels of arsenic, normally less than 0.25 mg/kg. However, rice and vegetables in Bangladesh as well as India are contaminated with high concentration of arsenic.

Seafood is the primary source of arsenic in the diet of Japanese and Spanish. Arsenic concentrations in seafood are 2.4-16.7 mg/kg in marine fish, 3.5 mg/kg in mussels (Buchet, 1994) and more than 100 mg/kg in certain crustaceans.

Speciation study shows that seafood in Japanese diet mainly contains arsenobetaine (47.9-75.2%). Others are inorganic arsenic (5.7-17.0%), monomethylarsonate (MMA; 1.1-3.6%), and dimethyl-arsinate (DMA; 6.6-27%; Yamauchi & Fowler, 1994).

Wine is also contaminated with arsenic when grapes are sprayed with arsenic containing pesticides (up to 500 ppb) in the As^{III} form (Hughes, 1994).

The daily intake of arsenic by the people of different countries is reported for comparison (Figure 1.3). Spanish showed the highest consumption of arsenic that is followed by Japanese, Indian and French. The data of Bangladeshi are not shown which may be similar to the Indians. High consumption of arsenic by Spanish or Japanese is due to high intake of seafood whereas by Indian or Bangladeshi is due to consumption of arsenic contaminated water.

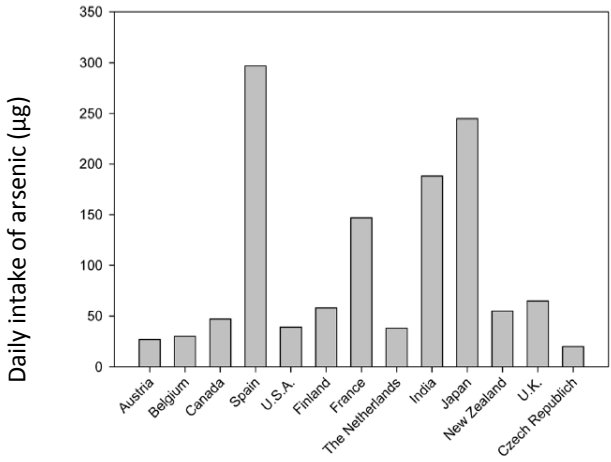


Figure 1.3 *Daily intake of arsenic by the people of different countries (Carbonell-Barrachina et al., 2009).*

Human body: In arsenic non-endemic areas, the level of arsenic in human blood is <1 ppb, urine <100 ppb, nails ≤1 ppm and hair ≤1 ppm (Table 1.3). The amount of arsenic in nail is comparatively higher than that of hair. Blood is the

principal vehicle for the transport of arsenic following absorption, and arsenic is cleared relatively rapidly from it. It is rather surprising that arsenic concentration, after entering into blood, remains very low. It may be due to rapid distribution in different tissues or rapid excretion. However, arsenic reduces the erythrocyte glutathione level indicating that while it stays in blood, it produces oxidative stress in erythrocytes. The mean reduced glutathione level in red blood cell of arsenic affected patient was 55.3 mg/dL, in arsenic exposed family member was 57.8 mg/dL, and in the control group was 88.7 mg/dL (Sinha et al., 2003).

Data on human body are mainly based on autopsy result. The muscles, bones, kidneys and lungs have the highest absolute amounts of arsenic, but skin and excretory/storage organs, such as nail and hair, have the highest concentrations. Tissue distribution of arsenic indicates that levels of arsenic in the kidneys, liver, bile, brain, skeleton, skin and blood are 2-25 times higher for the As^{III} than for the As^{V} form and are greatly increased at higher doses.

1.6 Prevalence

Over 226 million people from more than 105 countries, from Bangladesh to Bolivia, are consuming high concentration arsenic (Murcott, 2012). The numbers of people affected in Asia are more than the rest of the world (Ravenscroft et al., 2009). The worst situation is in Bangladesh and India (West Bengal). Most of them are from drinking water of groundwater source. In Latin America, 14 out of 20 countries are affected with high concentration of arsenic in drinking water with total exposed people of about 14 million (Bundschuh et al., 2012). The exact number of cases of arsenicosis is not known. The countries having large number of arsenic exposed people and cases of arsenicosis are described below:

Bangladesh: Bangladesh is a densely populated area. Its total population is 157 million. About 95% of total population is using groundwater for drinking and cooking purposes. People of urban areas are using water of deep aquifer whereas hand pumped tube wells are used by rural people. There are in total 8.6 million hand pump tube wells (?) of which 4.7 millions are screened for arsenic mainly by ket methed. Although kit method is not a reliable method, the data shows that 1.4 million hand pumped tube wells are contaminated with more than 50 ppb arsenic (Unicef, 2008). There are more than 8,000 villages (total number of villages within the country: 87,319) where 80% of all hand pump tube wells are contaminated.

About 36 million people are consuming arsenic contaminated drinking water (>10 ppb) of hand pump tube wells (Chakraborti et al., 2010). This data is based on 52,202 water samples throughout the country analyzed by flow injection hydride generation atomic absorption spectrometry. Estimation of total arsenic by atomic absorption is more reliable than kit method. About 43% of the estimated hand pump tube wells contain arsenic >10 ppb (Table 1.5). The amount of arsenic above 300 ppb is about 6%. The water of deep tube wells is also contaminated. Multiple Cluster Indication Survey of 2009 conducted a survey in 15,000 households across Bangladesh and showed 7.7% deep tube wells were contaminated with unsafe concentration of arsenic (Unicef, 2011). More than 90% of drinking water is as As^{III} (Huq & Naidu, 2003).

Sixty out of total 64 districts of Bangladesh are affected by arsenic contaminated drinking water. Area wise distribution of arsenic contaminated drinking water is clearly shown only in Bangladesh. High levels of arsenic in groundwater occur in the districts of Chandpur, Comilla, Noakhali, Munshiganj, Brahmanbaria, Faridpur, Madaripur, Gopalganj, Shariatpur, and Satkhira. Irrigation of cultivated land with arsenic contaminated water has polluted the

soil leading to the presence of arsenic in foodstuffs.

Table 1.5 *Percentage of hand pump tube wells containing different concentrations of arsenic in water.*

Concentration of arsenic (ppb)	Percentage of tube wells
<10	57.0
10-50	15.8
51-99	7.1
100-299	12.4
300-499	4.3
500-699	1.8
700-1,000	1.0
>1,000	0.5

(Chakraborti et al., 2010)

According to the report of the Directorate General of Health Services, Government of Bangladesh, 50,000 people are suffering from non-malignant skin lesions of arsenicosis. In reality, the number will be 2-3 times more which is due to poor statistical data. The capital city Dhaka is supplied by tap water which is not contaminated but the people (about 15 million) living within the city are consuming foodstuffs which are supplied from some of the arsenic endemic areas.

Only a few cohort studies have been done in Bangladesh. A study conducted at Matlab, Bangladesh (an arsenic endemic area) shows that there were 504 confirmed cases of non-malignant skin lesion of arsenicosis among the total population of 166,934 (>4 years of age). That is, 3 per 1,000 are affected by arsenicosis (Rahman et al., 2006). A cross-sectional study in another arsenic endemic area in Bangladesh shows that there were 714 cases of non-malignant skin lesion among 11,438 subjects (Argos et al., 2007). The incidence rate is 6.2%. That is, the incidence rate in two arsenic endemic areas varies a wide range. A study conducted by the Massachusetts Institute of Technology (MIT) estimated the arsenic health burden through a model of dose-response function (Yu et al., 2003). The research group predicted that long-term exposure will

result in approximately 1 million cases of melanosis, 350,000 cases of keratosis, 8,500 cases of skin cancer, and 6,500 fatalities per year from internal cancer (Table 1.6). Among the arsenic-induced fatal cancers, males will be more affected than female.

Table 1.6 *Estimated health impact of arsenic contamination of tube well water in Bangladesh.*

Illness	Males	Females	Combined
Fatal cancer/year	3,809	2,718	6,528
Non-fatal cancer/year	1,071	1,024	2,095
Total number of cancer fatalities accumulated over 50 years	190,450	135,900	326,400
Arsenicosis			
Hyperpigmentation	654,718	316,511	971,230
Keratosis	277,759	74,473	352,233
Cough	21,823	68,887	90,712
Breathlessness	93,247	176,874	270,122
Glucosuria	67,887	63,551	131,439
Hypertension	94,396	88,366	182,762
Total arsenicosis cases in each year	1,209,830	788,662	1,998,498

(Koundouri, 2005; Maddison et al., 2004)

Among the non-malignant skin lesions, all the patients have melanosis and leucomelanosis. About 50% have keratosis. It is rare where the patient is suffering from keratosis without melanosis or leucomelanosis. Only a few cases of Bowen's diseases are reported. The number of reported skin cancer due to arsenic is low. Latency period of symptoms are 10-15 years. One study shows that on average, 16.6% of arsenicosis had died of cancer during the last 9-12 years (Chakraborti et al., 2010). There is dose-response relationship between inorganic arsenic exposure and risk of hypertension (Rahman et al., 1999).

India: The total population in India is 1,256 million. The states of West Bengal, Bihar, Jharkhand, Uttar Pradesh, Assam, and Manipur are reported to be contaminated with high concentration of arsenic in drinking water. West

Bengal is the most severely affected area. The total number of Indians consuming high concentration of arsenic is not clear.

West Bengal – Out of 19 districts, 9 districts of West Bengal are severely affected by arsenic contaminated drinking water. Badly affected districts are Malda, Murshidabad, Nadia, North-24-Parganas, South-24-Parganas, Bardhaman, Howrah, and Hoogly. About 26 million people of West Bengal are exposed to high concentration of arsenic (Chakraborti et al., 2009). On the basis of estimating arsenic level of 140,150 hand pump tube wells using atomic absorption spectrometer, about 50.1% of tube wells contain more than 10 ppb (Table 1.7; Chakraborti et al., 2010). The amount of arsenic above 300 ppb is about 3.4%. The extent of arsenic contamination is more or less similar to Bangladesh. Screening of 86,000 people show that 8,500 people were suffering from arsenicosis (9.7%; Chakraborti et al., 2002). The same research group reported that about 300,000 cases of arsenicosis with symptoms of non-malignant skin lesion are present in West Bengal (Chakraborti et al., 2002).

Table 1.7 *Percentage of hand pump tube wells containing different concentrations of arsenic in West Bengal.*

Amount of arsenic (ppb)	Percentage of tube wells
<10	49.9
10-50	26.2
51-99	9.3
100-299	11.2
300-499	2.3
500-699	0.7
700-1,000	0.3
>1,000	0.1

(Chakraborti et al., 2009)

Bihar – The total population in Bihar is 50 million. In total, 7,218 out of 27,061 hand pump tube wells were tested which had arsenic concentration of

more than 10 ppb. That is 26.7% tube wells are contaminated. The water contains high concentration of As^{III} (87%). More than 13.85 million people are drinking high arsenic contaminated water (>10 ppb) in Bihar. Out of 38 districts, 16 districts are severely affected by arsenic contaminated drinking water. Among them the badly affected districts are Bhojpur, Buxar, Vaishali, Bhagalpur, Samastipur, Khagaria, Katihar, Chapra, Munger and Darbhanga. Non-malignant skin lesions of arsenicosis are mainly reported. In addition, there are non-pitting edema, liver and kidney disorders.

Jharkhand – Only 320 villages were screened in December 2003 and 30% of the hand pump tube wells had arsenic concentration >10 ppb. Only 87 cases were diagnosed as arsenicosis (Mukherjee et al., 2006).

Uttar Pradesh – The total population of Uttar Pradesh is 166 million. Only three districts (Ballia, Gazipur & Varanasi) out of 70 districts were screened. About 45% of the hand pump tube wells are contaminated with arsenic (>10 ppb; Ahamed et al., 2006). The number of patients is only 154.

Assam – A survey conducted (between 2005 and 2010) jointly by the State Public Health Engineering Department, UNICEF and the IIT, Guwahati showed that 7,22,603 people of 18 districts (out of 24 districts) are at risk of chronic arsenic poisoning. The affected districts are Goalpara, Dhubri, Bongaigaon, Barpeta, Nalbari, Kamrup, Darrang, Sonitpur, Lakhimpur, Sivasagar, Jorhat, Golaghat, Nagaon, Morigaon, Cachar, Hailakandi, Karimganj and the BTAD areas. The total number of arsenicosis is 2,581.

In Chandigarh and adjacent areas, high concentration of arsenic (>500 ppb) is present not only in hand pump tube wells but also in surface water like ponds and canals.

There is 6-fold increased risk of stillbirth following exposure to high

concentrations of arsenic (200 ppb) during pregnancy (von Ehrenstein et al., 2006). No association was found between arsenic exposure and spontaneous abortion or overall infant mortality. Women had lower risks than men of developing skin lesions and showed little evidence of respiratory effects (shortness of breath at night, morning cough in smokers and shortness of breath in nonsmokers; von Ehrenstein et al., 2005).

China: The total population in China is 1,387 million. The Chinese government in 1994 declared arsenicosis as an endemic disease throughout the nation and conducted a massive screening program to sample wells in about 12 per cent of the counties. Because of the large size of China, it will take several decades to complete the screening of million of wells to determine the spatial occurrence and magnitude of arsenic contamination throughout the country. The total area at risk is around 580,000 km^2 (about 4 times the size of Bangladesh).

The affected areas include 8 provinces (Xinjiang, Inner Mongolia, Shanxi, Guizhou, Henan, Jilin, Ningxia, and Qinghai provinces) and 37 counties in China. The population exposed to high concentration of arsenic is estimated to be more than 20 million, and more than 30,000 arsenicosis cases have been confirmed. Drinking water of hand pump and deep tube wells are contaminated with arsenic.

In southwest China, arsenic-rich coal is used to dry chili peppers and corn, exposing people to arsenic both through inhalation and by contaminating food. Coal in Guizhou has undergone mineralization and thus produces high concentrations of arsenic. However, arsenic concentrations in the drinking water are within the normal range. The estimated sources of total arsenic exposure in this area are from arsenic-contaminated food (50-80%), air (10-20%), water (1-5%), and direct contact among coal-mining workers (1%). The use of arsenic-contaminated coal in some areas in Guizhou Province of China is also

responsible for contamination. At least 3,000 arsenicosis cases were found in the Southwest Prefecture of Guizhou, and approximately 200,000 imhabitants are at risk for such over exposures (Liu et al., 2002).

The estimated arsenic intakes from rice and calculating the associated excess cancer risk for the Chinese population is to be 152 per 100,000 (Meharg et al., 2009).

Chile: The total population in Chile is 17 million. The cities having the highest exposure to arsenic are Antofagasta, Calama, Santiago, Ancagua, Taltal, Tocopilla and San Pedro de Atacama. Approximately 500,000 inhabitants are exposed to arsenic contamination. Lung and bladder cancer mortality rate increases about 10 years after high arsenic exposure commenced and continued to rise until peaking in 1986-1997 (Marshal et al., 2007). In this population, arsenic in water contributed more to mortality than did cigarette smoking.

People exposed to very high concentration of arsenic (averaging between 500 and 600 ppb) drinking water back in the 1950s and 60s are still showing a higher-than-normal risk of cancer of urinary bladder or lungs, years after the arsenic problem was brought under control. In Antofagasta, the incidence of urinary bladder cancer (2009) among men was about 16 cases per 100,000 while it was under six per 100,000 for the rest of Chile. Females suffer in less in number. It was 13.5 cases for every 100,000 women while it was 2.5 per 100,000 in the rest of Chile. At the peak, arsenic-induced cancers were responsible for the deaths of 1 in 20 females, and 1 in 10 males.

Like Taiwan, blackfoot disease is also reported in Chile (Borgono et al., 1997).

Argentina: The total population in Argentina is 41 million of which about 2 million people are exposed to high level of arsenic. The affected provinces are Cordoba, Salta, La Pampa, Santa Fe, Tucuman, Santiago del Estero, San Luis,

and parts of Buenos Aires which are four times larger than the Bengal-basin area (India and Bangladesh) (Nicolli et al., 2012). The most important effects of arsenicosis are keratosis, warts, melanosis, leukomelanosis, basal cell carcinoma and cancer of the urinary bladder. It has been shown that arsenical keratosis predominates over melanosis. The types of cancer found were skin cancer and internal cancers (66% of which were in the lungs).

Taiwan: The total population in Taiwan is 23 million. In limited areas of southwest coast of Taiwan, 100,000 inhabitants used artesian well water containing high concentration of arsenic (mainly As^{V}, small amount of As^{III}; Wang et al., 2001) from 1920s to 1970s. A survey on 40,421 inhabitants in 37 villages in the affected area showed 18.5% had skin manifestations of arsenicosis.

About 30,000 cases have been identified as arsenicosis (Sun, 2001). The new cases of blackfoot disease were rarely reported since 1970 when tapewater was used for drinking instead of groundwater. Since 1990, no more new cases of blackfoot disease were reported.

The blackfoot disease was prevalent before 1970 in the southwest coast of Tainan, especially in Beimen, Hseuchia, Jiangjing and Yenshui Townships of Tainan County as well as Budai and Yichu Townships of Chiayi County. There were 1,455 reported cases of blackfoot disease in Tainan from 1954 to 1977 (Cheng, 1977).

Melanosis, keratosis and skin cancers were found among people who drank from arsenic contaminated wells water (but no effect was seen below 150 ppb, which might therefore be a biological threshold) and a very high incidence of lungs, bladder and other cancers was found (Chen et al., 1986). The prevalence of melanosis (18.4%), keratosis (7.1%) and skin cancer (1.1%) in the arsenic

endemic area was high (Tseng et al., 1968). There were increasing water arsenic concentrations (170, 470, and 800 ppb) resulted in mortality rate ratios for lung cancer of 1.8, 3.3, and 4.5 for males, and 2.8, 4.3 and 8.8 for females, respectively, using lungs cancer mortality in the general Taiwanese population for comparison. Overall prevalence rate in 1968 was 0.89% (Tseng et al., 1968).

Mexico: The total population is 122 million. It is estimated that around 450,000 people are exposed. In Mexico, the amount of arsenic contaminant in groundwater varies from 10 to 5,000 ppb (Del Razo et al., 1990). The presence of arsenic in drinking water is severe in Durango, Coahuila, Zacatecas, Morelos, Aguas Calientes, Chihuahua, Puebla, Nuevo Leon, Guanajuato, San Luis Potosi and Sonora aquifers and the Lagunera region. More than 50% of the potable drinking water in the Lagunera Region of northern Mexico have arsenic concentrations >50 ppb (Del Razo et al., 1990). The predominant type of arsenic in 90% of the samples was As^{V}. The prevalence of blackfoot disease in Mexico is 0.7%.

Peru: The total population in Peru is 30 million. Traces of arsenic have been found in some of the rivers; for example, the River Locumba (500 ppb), which flows through Puno and Moquegua (the Ilo valley), where approximately 250,000 inhabitants are exposed to arsenic.

USA: It is estimated that 13 million Americans live in areas where the concentration of arsenic in public water supply exceeds >10 ppb. Arsenic concentrations found in at least 25% of groundwater samples based on 31,350 samples in each county (Ryker, 2001). Arsenic concentrations in groundwater are generally highest in the west. Parts of the midwest and northeast also have arsenic concentrations >10 ppb. Arsenic concentrations appear to be lower in the southeast, based on a smaller amount of data. Even at sampled locations, concentrations might differ between hand pump and deep tube wells water.

These data illustrate how arsenic concentrations vary across broad regions of the country.

Exposure to 50 ppb of arsenic in drinking water can cause 31 cases of skin cancer per 1,000 inhabitants.

Nepal: The total population in Nepal is 28 million. Maximum concentration of arsenic in hand pump tube wells of Nawalparasi, Bara, Parsa, Rautahat, Rupandehi, and Kapilvastu districts were 571, 254, 456, 324 and 2,620 ppb, respectively (Maharjan et al., 2006). The population at risk for arsenicosis was estimated to be 3.5 million (Pokhrel et al., 2009). About 5,000 cases of arsenicosis are suffering symptoms of melanosis and keratosis on the palms, trunk, and soles of the feet (Nepal, 2011). Nawalparasi is the most affected district among those six districts, where about 3.6% people have prevalence of arsenicosis.

Pakistan: The total population in Pakistan is 183 million. The arsenic (>10 ppb) affected provinces are Punjub (about 20% population) and Sindh (about 36% population) (Ahmed et al., 2004).

Punjab – In Punjab, 18 districts out of 34 had arsenic contamination in both hand pump and deep tube wells water (>50 ppb). 36,000 samples were estimated for arsenic of which 31% contain 10-50 ppb, while 9.0% had arsenic over 50 ppb. Maximum arsenic contaminated samples 250-500 ppb found in southern and eastern Punjab. More than 65% of the people living in Lahore are consuming water contaminated with arsenic. Southern Punjab is facing serious threat which is causing cancer, stillbirth, post-neonatal mortality and other diseases. A study shows that about 28,000 people in seven districts of the Punjab had elevated arsenic in finger nails of people drinking >50 ppb. The prevalence rate of arsenicosis is 0.1%. It was estimated that 6 million people in

the Punjab drink water with arsenic level >10 ppb (Ravenscroft et al., 2009).

Sindh – High contamination of arsenic over 1,000 ppb has been found in two central districts in Sindh. About 23% tube wells in Khairpur district are contaminated with arsenic and the prevalence of melanosis and keratosis is 13 and 3.4 per 1,000 (Fatmi et al., 2009).

Cambodia: The total population in Cambodia is 15 million. Arsenic contamination of the Mekong River and groundwater is putting million of residents at risk of developing arsenicosis. Arsenic contamination of groundwater has been identified in at least 10 provinces of Cambodia with Kandal being one of the most heavily impacted. Six provinces were found to have elevated arsenic risk: Kampong Cham, Kampong Chnang, Kampong Thom, Kandal, Kratie, and Prey Veng. Over 100,000 people are at high risk in Kandal Province of Cambodia.

Levels in some areas approach 3,500 ppb. In total 320,000 people are at risk of arsenicosis. The groundwater arsenic pollution in the Mekong delta ranged up to 1,610 ppb in Cambodia (average 217 ppb) (Berg et al., 2007).

Vietnam: The total population in Vietnam is 88.8 million. Both Red River Delta (flat plain formed by the Red River) and Mekong Delta (region in southwestern Vietnam where the Mekong River approaches and empties into the sea) are affected. The groundwater arsenic pollution in the Red River Delta is up to 3,050 ppb (average 159 ppb) whereas it is up to 845 ppb (average 39 ppb) in the Mekong delta of southern Vietnam (Berg et al., 2007). The population at risk of arsenicosis is estimated to be 10 million in the Red River delta and 0.5-1 million in the Mekong delta.

Thailand: The total population in Thailand is 67 million of which 250,000 people are exposed to high concentration of arsenic. The prevalence of skin

manifestation from arsenicosis is 26.3% in Ronpibool district (Ekpalakom & Rodcline, 1994). It can be estimated that there would be around 5,000 cases of non-malignant skin lesions of arsenicosis and more than 10,000 people had arsenic levels higher in hair and nail. More than two-thirds of the drinking water supplies were contaminated with arsenic and about 2% had an arsenic level higher than the safety limit. Another study shows high arsenic intake from cooked food with the level of 726.8 μg/person/day.

Iran: Some villages in Kurdistan and West Azerbaijan provinces of Iran are contaminated with high concentration of arsenic in drinking water (maximum concentration: more than 1,000 ppb; mean concentration 290 ppb). Patients show skin lesions-keratosis, pigmentation, and even blackfoot disease in some villages.

Hungary and Romania: Groundwater resources in the Pannonian Basin (Hungary, Romania, Croatia and Serbia) are known to contain high concentration of arsenic (>10 ppb). Published data show that nearly 500,000 people are exposed through drinking water, making it the largest area so affected in Europe (Rowland et al., 2011). An estimated 300 Hungarians die each year as a result of consuming arsenic-contaminated groundwater.

In conclusion, Table 1.8 shows the most affected 25 countries of arsenic contamination of drinking water with number of arsenicosis cases.

The relative risks of lung cancer were higher in Taiwan where exposures were higher and of longer duration than in Chile. Lower relative risks were found in Argentina where exposures were lower.

Table 1.8 *Top 24 countries with areas where water is contaminated with high concentrations of arsenic.*

Sl. No.	Country	People exposed to arsenic	Area	Number of arsenicosis
1	Bangladesh	36 million	Chittagong coastal plain, Bengal basin	50,000
2	India	26 million	West Bengal, Assam, Nagaland, Thoubal (Manipur), Tripura, Chennai, Vapi (Gujarat), Chandigarh, Himachal Pradesh, Uttar Pradesh, Bihar	300,000
3	China	20 million	Xinjiang, Inner Mongolia, Henan, Shandong and Jiangsu provinces	30,000
4	Pakistan	6 million	Sindh (Indus plain), Punjab (Indus plain and valleys of tributaries)	
5	Vietnam	5.8 million	Red River, Mekong river delta	
6	Nepal	3.5 million	Terai, Kathmandu valley	5,000
7	Argentina	2 million	NW Argentine Andean highland, e.g. San Antonio de Los Cobres and many other localities, Chaco plain, Pampa plain, Copahue	
8	Ukraine	1.6 million	Cities of Donets, Makeevka, Yasinovataya	
9	Chile	500,000	Antofagasta, Calama, Santiago, ancagua, Taltal, Tocopilla and San Pedro de Atacama	
10	Hungary, Romania, Croatia and Serbia	500,000	Pannonian Basin	
11	Mexico	450,000	Durango, Coahuila, Zacatecas, Morelos, Aguas Calientes, Chihuahua, Puebla, Nuevo Leon, Guanajuato, San Luis Potosi and Sonora aquifers and the Lagunera region	
12	Laos	400,000	Mekong river plain	
13	USA	350,000	Appalachian Highlands; Massachu-setts to Maine, Appalachian Highlands; NE Ohio, Interior Plains: E Michigan, Interior Plains: Upper Midwest, Interior Plains: NE Wiscon-sin, Interior Plains: Upper Midwest, Interior Plains: Upper Midwest, Interior Plains: S Dakota, Interior Plains: central Oklahoma, Rocky Mountains: Yellowstone National Park, Intermontane Plateaus: Oregon, Intermontane Plateaus: Carson desert, Nevada, Pacific Mountain System, Pacific Mountain System: NW Washington, Pacific Mountain System,	

Sl. No.	Country	People exposed to arsenic	Area	Number of arsenicosis
			Pacific Mountain System: Arizona, Pacific Mountain System: southern San Joaquin valley, Arizona; Fairbanks, Alaska, Akutan island (Aleutian islands), Kilahuea, Hawai, Soda Dam/Valles Caldera (Manzano Mountains), New Mexico, SW Florida between Tampa and Ft. Myers	
14	Cambodia	320,000	Mekong river delta	
15	Peru	250,000	Puno, Ilo	
16	Thailand	250,000	Hat Yai, Nakorn Chaisi, Rhon Phibun district, Tin belt (Naknon Si Thammarat province)	2,000
17	Colombia	180,000	Caldas, Departments of S Tolima, Nariño	
18	Mongolia	99,000	Govi Altai-Hovd, Arkhangai, Dornod steppe	1,774
19	Bolivia	20,000	El Alto (La Paz), Oruro, Poopó basin, North of Potos ídept., Lipéz and south of Potos ídept.	
20	Indonesia		Citarum river, Aceh	
21	Iran		Kurdistan	
22	Japan		Shinji plain, Fukui, Niigata plain, Sendai, Takatsuki, Osaka, Kyushu island	
23	Kazakhstan		S Mangyshlak	
24	Taiwan		Guandu plain, Lanyang plain, Chianan plain	
25	Turkey		Emet-Hisarcik area, Afyon, Heybeli spa, Izmir province	

After several years of low level arsenic exposure, various non-malignant skin lesions appear. These are manifested by melanosis, leucomelanosis and keratosis. After a dozen or so years skin cancers may develop. Twenty or thirty years after exposure to 500 ppb of arsenic, internal cancers (lung, kidney, liver and bladder) appear among 10% of all exposed.

Basal cell carcinoma is the most frequent type of among Euro-Americans, whereas Bowen disease is the most frequent type among Asians (Abernathy et al., 1999).

At low doses, the risk of cancer is assumed to be linear and lifetime exposure at 10 ppb is predicted to result in 6 excess skin cancer cases per 10,000 people exposed (6×10^4). This is relatively high risk for drinking water; risk targets are usually fixed at one additional death per 100,000 people exposed (1×10^5). The US National Academy of Sciences has noted that as many as 1 in 100 (1×10^2) additional cancer deaths could be expected from a lifetime exposure to drinking water containing 50 ppb arsenic.

1.7 Double Edged Sword

Chronic consumption of arsenic may lead to cancer particularly skin cancer. On the other hand, it is still an effective drug for the treatment of chronic promyelocytic leukemia. Its dual role is not clear. Like arsenic, beta-carotene, retinol also act as a double edged sword. Here, dose may be a factor that is not yet established.

Lifetime risks of dying cancer from arsenic in tap water of the USA are shown in Table 1.9.

Table 1.9 *Lifetime risks of dying cancer from consuming tap water with arsenic.*

Concentration of arsenic (ppb)	Approximate total cancer risk
0.5	1 in 10,000
1	1 in 5,000
3	1 in 1,667
4	1 in 1,250
5	1 in 1,000
10	1 in 500
20	1 in 250
25	1 in 200
50	1 in 100

Assuming arsenic contaminated water of 2 liters consumed per day (Based upon the National Academy of Sciences' 1999 Risk estimates).

1.8 Biomarker of Arsenicosis

Estimation of total arsenic in urine, hair, and nail are usually used to confirm the diagnosis of arsenicosis. These samples can be easily collected from the patient. Still now no dependable biomarker is identified.

Presence of arsenic in urine indicates the recent exposure of arsenic whereas high amount of arsenic in hair or nail indicates long-term exposure to arsenic.

In absence of dependable marker, the diagnosis of arsenicosis involving organs other than the skin is difficult to confirm. How many people are suffering from arsenicosis is still not yet known.

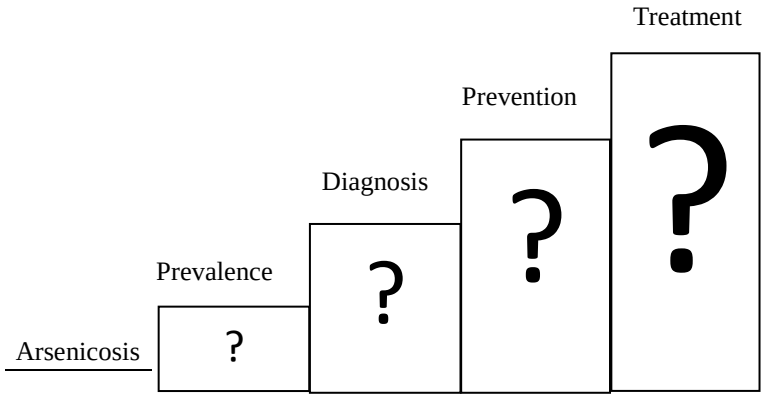
1.9 Providing Arsenic Safe Drinking Water

Since 1993 international donor agencies mobilized fund to Bangladesh. Extensive researches were conducted how to provide arsenic safe drinking water. Several methods were suggested, but none is suitable for the Bangladeshi arsenicosis with non-malignant skin lesions. There are more chances of bacterial infection using these options for providing arsenic safe drinking water.

1.10 Vitamins and Minerals

Retinol, ascorbic acid, alpha-tocopherol, zinc, and selenium are either alone or in combination is considered to be effective in reducing non-malignant skin lesions. Prolonged duration of treatment is required ranging from 6 to 14 months. These all are antioxidants. Antioxidants in high doses may serve as pro-oxidant. Stoppage of supplementation of these vitamins and minerals recur the symptoms.

1.11 Big Questions



The prevalence of arsenicosis is not clear. A small question mark is determined by this aspect. It is much more complicated task to diagnose the cases if the patient has no melanosis or keratosis. About prevention of disease, a number of approaches were tried. Extensive works were done. But not a single one is appropriate for Bangladeshi. Some antioxidant vitamins and minerals were identified to be effective, but their role in the total cure shows big question.

A group of authors wrote a book "The Taiwan Crisis: A showcase of the global arsenic problem" (Jean et al., 2010). They wrote:

In the 1950s, the residents of the southwestern coastal areas of Taiwan suffered greatly from blackfoot disease due to the consumption of arsenic-contaminated groundwater. Groundwater with high levels of arsenic in southwestern and northeastern Taiwan received much attention. After arsenic-safe tap water was utilized for drinking instead of groundwater in the 1970s, blackfoot disease cases decreased greatly. After 1990, no new blackfoot disease cases were reported, and as a consequence, blackfoot disease problems disregarded. However, arsenic is still present in the groundwater.

The title of this book should be “The Bangladeshi Crisis: A mummified case of the global arsenic problem”. It is not a joke. It is real as because:

During 1997-1998, two specialists from World Bank and WHO came to Bangladesh to assess the situation. Subsequently considerable research funds were mobilized. Most of the research funds were used to provide arsenic safe drinking water. Only a small fraction of funds were utilized in health issues of arsenicosis. At present the flow of funds is almost nil (Adams, 2013) and research activities are also related to the fund. However, the number of diagnosed patients is increasing.

The limitations of the studies are a) group rather than individual measures of drinking water arsenic; b) lack of biomarkers to confirm arsenic exposure; and c) the underestimation of confounders such as cooking water and contaminated food (Wang et al., 2007).

1.12 Questions to be Raised

1. High concentration of arsenic was found in the mummified human body as long as 7,000 years, but arsenic was used as medicine for at least 2,500 years. Why is such discrepancy?

2. Arsenic causes cancer in skin, lungs and urinary bladder. Is it due to exposed part of these organs?

3. Previous exposure of arsenic may cause cancer. When a population of an arsenic endemic area is already exposed to arsenic, is it necessary to take preventive measure of arsenic exposure?

4. The amount of arsenic in water is closely related to the effect. What is the role of arsenic in food?

5. Prolonged exposure means 6 months or more. What is the scientific basis of this criterion.

6. In West Bengal (India), 26 million people are exposed to high concentration of arsenic of which 300,000 shows arsenicosis (non-malignant skin lesions). On the other hand, 36 million Bangladeshi are exposed to arsenic of which 50,000 are suffering from arsenicosis (non-malignant skin lesions). Why?

7. Why the involvement of liver in arsenicosis of Indians are more than Bangladeshi patients?

8. Why the cases of blackfoot disease are limited in Taiwan and a small extent in Chile and Mexico? Is there any relationship between the ratio of As^{III} and As^{V} in drinking water in the development of blackfoot disease?

9. Is there any regional variation in the development of skin cancer and the concentration of arsenic in drinking water. For example, ingestion of 50 ppb of arsenic in drinking water can cause skin cancer among Americans but not among Bangladeshi.

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Chapter

2

〖Risk Factors of Arsenicosis〗

It is mentioned that all the members of a family are consuming arsenic through same source of drinking water and foodstuff but all do not show skin manifestations. One or two of them show skin manifestations. The reason is not clear. Therefore, researchers are trying to identify risk factor(s) for arsenicosis. Better understanding of the risk factor(s) could help to reduce the number of cases of arsenicosis. The studied factors are age, gender, nutritional status, tobacco smoking, alcohol, betel nut use, exposure to sunlight, pesticide or fertilizer, liver dysfunction, keratosis or Bowen's disease.

2.1 Age

Early non-malignant skin manifestations of arsenicosis are not uncommon in children below 10 years. Approximately 90% of children below 11 years of age living in arsenic endemic areas show hair and nail arsenic level above the normal level. The youngest arsenic poisoned patient detected in Bangladesh was an 1.5 years old child. In the Antofagasta region of Chile, cases of non-malignant skin lesion of arsenicosis have been described in children as young as 2 years of age (Rosenberg, 1974; Zaldivar & Guillier, 1977). In Taiwan, the youngest patient drinking arsenic contaminated water who developed melanosis was 3 years old (USEPA, 1988).

Children appear to have a higher body burden than adults despite fewer dermatological manifestations (Rahman et al., 2001). The status of mental development in children is affected in the age group of 1-5 years (Akhtar et al., 2007) and 9.5-10.5 years (Wasserman et al., 2004).

Studies on arsenic-induced health effects in Matlab, Bangladesh, showed that the highest prevalence of arsenic-induced skin lesions occurred in middle-aged men (Rahman et al., 2006).

There are inconsistent results associated with age and arsenic metabolism.

2.2 Gender

Gender issue may be considered on the basis of incidence and severity of arsenicosis as well as geographical variation.

About incidence, conflicting results are obtained from different studies. Some researchers reported that males and females are equally affected (Ahsan et al.,

2000; Hadi and Parveen, 2004) whereas others showed higher incidence in males (Tseng 1977; Guha Mazumder et al., 1998; Tondel et al., 1999; Ferreccio et al., 2000; Watanabe et al., 2001; Kadono et al. 2002; Sinha and Misbahuddin, 2003; Chen et al., 2003; Rahman et al., 2006; Table 2.1). However, another study shows females are more affected than males (Ahmad et al., 1999). These conflicting findings are due to improper study design and low number of cases. Even the same researcher group conducted studies in two different areas show inconclusive results.

However, gender-related exposure to arsenic is clearly interpreted in certain industries, e.g., mining and smelting operation (mainly men), wood preservation (mainly men), and electronic industries which are using gallium and indium arsenide (often women; Vahter et al., 2007).

About severity, keratosis and pigmentation changes may be worsen for women than for men, particularly in poor families (Alam et al., 2002).

Considering mean lifetime arsenic exposure, males had twice the risk of obtaining skin lesions as females in the highest exposure quintile (Rahman et al., 2006).

Higher incidence and severity of skin lesions in males may be due to more sunlight exposure, smoking habit, large volume of water intake and genetics. An involvement of hormone interactions is possible, because arsenic has been shown to interact with estrogen (Kitchin & Wallace, 2005) which affects all the cell types of importance for skin physiology (e.g., epidermal keratinocytes, dermal fibroblasts, melanocytes). In addition, differences between the sexes in the metabolism of arsenic might have influenced the likelihood of developing skin lesions. Women have higher arsenic methylation efficiency than men, but only in childbearing age, supporting an influence of sex hormones (Lindberg et

al., 2008).

Table 2.1 *Some examples of incidence of male and female patients of non-malignant skin lesions.*

Study	Country	Clinical manifestation	Incidence (n)	
			Male	Female
Tondel et al. 1999	Bangladesh	Melanosis with or without keratosis	279	151
Ahsan et al., 2000	Bangladesh	Melanosis with or without keratosis	50%	50%
Hadi and Parveen, 2004	Bangladesh	Melanosis with or without keratosis	26	22
Seow et al., 2012	Bangladesh	Melanosis with or without keratosis	340	210
Milton et al., 2004	Bangladesh	Melanosis with or without keratosis	59	79
Sinha et al., 2003	Bangladesh	Melanosis with or without keratosis	11	1
Ahmad et al., 2007	Bangladesh	Melanosis with or without keratosis	600	524
Guha Mazumder et al., 1992	India	Melanosis with or without keratosis	25	28
Hsueh et al., 1997	Taiwan	Skin cancer	24/275	9/379

However, the males and females have similar urine arsenic concentrations (Rahman et al., 2006). Compared with females, males often have a higher fraction of the MMA in urine (Hopenhayn-Rich et al., 1996), which has been associated with increased risk of arsenic-related skin lesions, including skin cancer (Chen et al., 2003; Del Razo et al., 1997).

Higher hemoglobin levels are significantly protective against the presence of skin lesions among Bangladeshi males but no such effect is seen in females (Breton et al., 2006).

2.3 Nutritional Status

Nutritional status of arsenicosis and unexposed normal volunteers is assessed

based on Body Mass Index (BMI), 24-recall or 3 days recall of major dietary contents. When BMI is lower than 18.5, then it is considered as malnutrition. However, BMI is not the only indicator for measuring nutritional status.

One study conducted in Bangladesh shows that BMI was lower than 18.5 in 57 (41.31%) out of 138 cases of arsenicosis and 31 (21.53%) out of 144 unexposed normal individuals. The crude prevalence ratio (or risk) was 1.92 for poor nutritional status among the arsenicosis cases compared to the unexposed population (Milton et al., 2004). In Bangladesh, more than 75% of the total populations suffer from anemia. Therefore, it is natural to think that millions of Bangladeshi should have non-malignant skin lesions of arsenicosis instead of thousands.

The prevalence of keratosis in West Bengal, India is 1.6 fold higher in poor nutritional status group (Guha Mazumder et al., 1998). Arsenic affected people of South Western Taiwan (Tseng 1977; Hsueh et al., 1995) and the Antofagasta region in Northern Chile (Borgono et al., 1977; Zaldivar & Guillier, 1977) were reported to have a low socio-economic status and poor nutritional status.

Skin lesions have been reported in well-nourished populations in Chile (Smith et al. 2000). Yang and Blackwell (1961) conducted a study of the diet and environmental conditions of a group of families in the arsenic endemic blackfoot area of Taiwan. Fish was the only notable source of animal protein in most cases studied. The researchers concluded that, in general, the diet was adequate with respect to calories, high in carbohydrate, low in protein, and extremely low in fat. Undernourishment in the Taiwan population was marked by a high consumption of dried sweet potato, a staple food that was significantly associated with an increased prevalence of arsenic-induced skin cancer (Hsueh et al., 1995).

In Taiwan blackfoot-disease was associated with undernourishment (high intake of sweet potatoes, low intake of rice and vegetables) (Chen et al., 1988). Low serum β-carotene concentration was associated with a higher prevalence of arsenic-related skin-cancer (Hsueh et al., 1997) and ischemic heart disease (Hsueh et al., 1998).

Hemoglobin concentration was not associated with non-malignant skin lesions (Heck et al., 2008). However, anemic rats are more prone to develop arsenic poisoning following chronic ingestion of high content of arsenic (Paul et al., 2002).

Deficiency in some nutritional factors may increase the risk of non-malignant skin lesions of arsenicosis. The strongest evidence was for low intake of animal protein, calcium, fiber, folate, and vitamin C (Mitra et al., 2004).

It has been reported that subjects with a poor nutritional status have a lower capacity for methylation and arsenic detoxication (Vahter & Marafante, 1987).

However, it is quite surprising that there was no study designed in such a way that all the family members of a case of arsenicosis were screened for malnutrition and found that poor nutriated family member was affected by arsenicosis.

2.4 Smoking

A positive correlation between ingestion of inorganic arsenic and lung cancer in humans was found in Chile (Ferrecio et al., 2000). It is already known that cigarette smoking is a main risk factor for lung cancer, but the researchers found that cigarette smoking plus ingestion of arsenic from drinking water had a synergistic effect (Ferrecio et al., 2000).

A study conducted in USA shows that there is an elevated risk of bladder

cancer in smokers that are exposed to arsenic in drinking water near 200 μg/L, compared with smokers consuming lower arsenic levels (Steinmaus et al., 2003). Arsenic is synergistic with smoking at relatively high arsenic levels (200 μg/L). The latency of arsenic exposure causing bladder cancer can be very long (more than 40 years). The risks were lower than those in Taiwan with high arsenic exposure (Morales et al., 2000).

There was a significant dose-response trend of ingested arsenic on lung cancer risk, which was more prominent among cigarette smokers. The risk assessment of lung cancer induced by ingested arsenic should take cigarette smoking into consideration (Chen et al., 2004).

A meta-analysis of studies on occupational arsenic exposure via inhalation found a synergistic effect of cigarette smoking and arsenic on lung cancer, and 30% to 54% of lung cancer cases were attributable to both exposures (Hertz-Picciotto et al., 1992). This effect was found to be stronger among those who smoked cigarettes, and the risk could be as high as more than 10-fold.

A study conducted in Bangladesh shows synergistic effect between the highest level of arsenic exposure (>113 ppb) and tobacco smoking on risk of skin lesions in men (Chen et al., 2006).

Smoking consumption might be associated with a poorer methylation capacity.

2.5 Alcohol

An alcoholic person may be exposed to arsenic contaminated water or alcohol sometimes contaminated with arsenic. Formar is applicable in arsenic endemic area where a person is used to drink alcohol. Peripheral vascular disease and cardiomyopathies were seen in a group of German vintners in the

1920s who drank wine fermented from grapes treated with arsenical fungicides (Engel et al., 1994). Arsenic was also found in sweet little Gabonese palm wine (Mavioga et al., 2009). Arsenic contaminated whiskey (moonshine) was found to cause cardiovascular diseases in Georgia, USA (Gerhardt et al., 1980).

Co-exposure of arsenic and ethanol elevates more significantly the activities of serum transaminases and induces more liver lesions than arsenic or ethanol alone (Flora et al., 1997). Alcohol consumption might be associated with a poorer methylation capacity.

2.6 Exposure to Sunlight

A study conducted in Bangladesh shows that the risk of skin lesions associated with any given level of arsenic exposure was greater in men with excessive sun exposure (Chen et al., 2006). Another study conducted in an arsenic-exposed area in Taiwan shows that skin cancer patients reported greater sunlight exposure than controls (Chen et al., 2003).

If sunlight exposure plays an important role, then there must be the chance of developing more skin lesions in the unexposed part of the body than the exposed part. Melanosis and leucomelanosis mainly present in the unexposed part of the body.

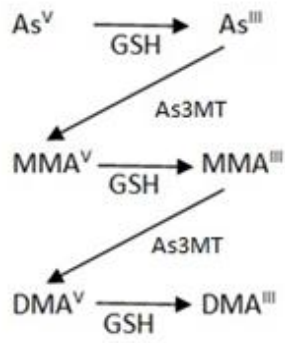
2.7 Exposure to Pesticide and Fertilizer

Most of the Bangladeshi consuming arsenic contaminated water are living at rural areas. A large percentage of them are either directly involved in cultivation or indirectly exposed to pesticides and fertilizers. Some of the pesticides are arsenic based (for example, Fudanon 10G in Bangladesh; Green plaster in West

Bengal, India). Foodstuffs are contaminated with these substances. A study conducted in Bangladesh shows that there is no influence of pesticide use in the relation between arsenic exposure and risk of skin lesions (Chen et al., 2006).

2.8 Liver Dysfunction

The main organ for arsenic metabolism is the liver. Methylation capacity might reduce with increasing dosage of arsenic exposure.



2.9 Melanosis and Cancer

A significant association between melanosis and liver cancer is not observed.

2.10 Keratosis and Cancer

A 67% increase in liver cancer risk is observed among subjects with skin cancers and keratoses, suggesting that a higher incidence of liver cancer should be expected among people with such skin signs.

Keratosis is significantly associated with an increased lung cancer risk. A significant interactive effect on lung cancer risk between keratosis and cigarette

smoking was identified, which suggests that patients with keratoses who have been exposed to arsenic should cease smoking (Hsu et al., 2013).

2.11 Bowen's Disease and Cancer

A significant association of Bowen's disease and nonmelanoma skin cancer with an increased lung, urinary tract, prostate, and other gastrointestinal cancer risk, but not with liver cancer. Keratosis is associated with increased lung cancer risk. The strong interaction between cigarette smoking and keratosis with or without skin cancer appeared to increase the risk of lung cancer significantly.

2.12 Questions to be Raised

1. Is there any relationship between nutritional status and the development of arsenicosis?
2. Whether poor nutritional status increases the susceptibility to arsenicosis, or alternatively that arsenicosis may be responsible to develop poor nutritional status.

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✶ Myth 1

Children are free from developing arsenicosis.

✶ Myth 2

Melanosis is due to high exposure to sunlight.

Chapter

3

〖Clinical Manifestations and Complications〗

"Peoples drinking high concentration of arsenic without any clinical manifestations are preclinical and should not be underestimated."

K. C. Saha, School of Tropical Medicine, Kolkata

Clinical manifestations of arsenicosis vary from country to country. Initial features following chronic exposure of arsenic are general malaise, weakness, general debility, decreased appetite, and weight loss (Hindmarsh, 2002). These symptoms are non-specific. After several months of exposure, non-malignant skin manifestations are usually developed. This may be the first indication of the internal organ's pathology. The clinical

manifestations that involving different organs (Table 3.1) following chronic consumption of arsenic are as follow:

Table 3.1 *Arsenicosis affecting different organs/systems.*

Organ/system	Health problem
Skin	Melanosis, leucomelanosis, keratosis, Bowen's disease, squamous cell carcinoma, basal cell carcinoma
Cardiovascular	Blackfoot disease, atherosclerosis, hypertension, ischemia, cardiac arrhythmia
Endocrine	Diabetes mellitus
Pulmonary	Bronchitis, bronchiectasis, chronic obstructive pulmonary disease, lung cancer
Reproductive	Low birth weight, stillbirth, spontaneous abortion
Urinary	Cancer of the urinary bladder
Gastrointestinal	Diarrhea
Hepatobiliary	Fatty liver, cirrhosis, enlarged and tender liver along with increased hepatic enzymes
Neurological	Neuropathy, mental retardation
Hematological	Anemia, leucopenia

3.1 Non-malignant Skin Lesions

The risk of non-malignant skin lesions increases both with duration of exposure and arsenic concentration. These include melanosis, leucomelanosis and keratosis. Either melanosis or leucomelanosis do not cause any ill feeling to the patient. However, keratosis in hand may cause ill looking. Melanosis is usually the common and the earliest symptom. Sometimes it is along with leucomelanosis and keratosis. The combination of melanosis and keratosis is sometimes called melanokeratosis. Keratosis is approximately half as common as melanosis. A study in China showed that 22% had typical keratosis on the palms or soles and some had melanosis and leucomelanosis on the trunk. In young adults melanosis usually shows no keratosis whereas in older people there was more or less keratosis and the skin per se was atropic and less elastic (Yeh et al., 1968).

Melanosis at oral mucosa (undersurface of the tongue, buccal mucosa), Mee's line, the patchy hair loss and non-pitting edema may be present.

Melanosis: Melanosis is also called hyperpigmentation or dyspigmentaton. Literally hyperpigmentation is caused by an excess production of melanin (brown pigment) which is produced by melanocytes at the lower layer of the epidermis. Melanosis is usually a harmless condition in which patches of skin become darker in color than the normal surrounding skin.

It is difficult to say exactly when or by whom melanosis was first reported following medicinal use of arsenic (Stockman, 1923).

Latency period (the duration of the patient's arsenic exposure with the date of onset of symptoms) of melanosis does not follow a particular time frame. It may be after drinking arsenic contaminated water for one year or even less in West Bengal, India (Garai et al, 1984; Guha Mazumder et al., 1997). The appearance of melanosis occurred within 6-12 months of the start of treatment with Fowler's solution at a dose of 4.75 mg/day.

In arsenic-induced melanosis, pigmentation varies in depth of color from a light mottled grey to black-brown. Melanosis may be diffuse, spotted or localized. Melanosis frequently appears on the unexposed part of the chest, back and limbs. The reason why it is not distributed throughout the whole skin is still not clear.

All the members of a family are drinking arsenic from the same source but all of them are not showing skin manifestations. There may be involvement of some compounding factors: age, gender, nutrition or other unknown factors. These are discussed in the previous chapter.

In addition to arsenisosis, other causes of hyperpigmentation are over exposure

of skin to sun light, heredity, picking at the skin, hormonal changes, and medications such as antibiotics, hormone treatments and antiseizure drugs; and inflammation and skin injuries such as acne vulgaris.

Leucomelanosis: There are areas of hypopigmentation in the skin (white/yellow spot), giving the appearance of raindrops (Figure 3.1). The area of white/yellow spot increases after stoppage of arsenic contaminated water. These areas of white/yellow were analyzed for leutin, a carotinoid as well as an antioxidant (Misbahuddin et al., 2008). There is increased accumulation of leutin in spots in comparison to other normal colored skin. That is, leucomelanosis is due to accumulation of leutin.

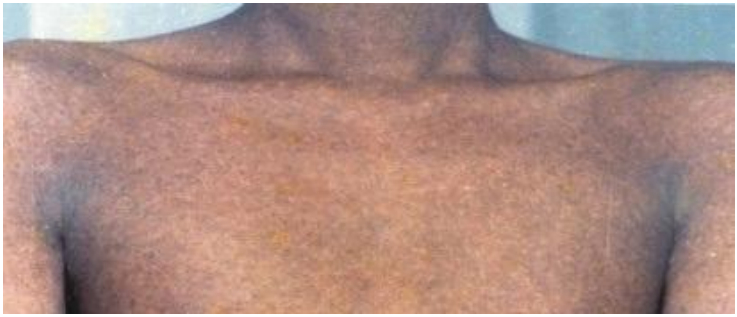

Figure 3.1 *Melanosis and leukomelanosis present in the skin of an arsenicosis individual (rain-drop appearance).*

Keratosis: Keratosis means the growth of keratin layer of the skin. It is often develops after melanosis. Keratosis occurs mainly in palms and soles. It may also appear at other parts of the body skin. It is surprising that Bangladeshi or Indian patients are suffering from keratosis that is only limited to palms and soles. If palm is affected, in that case both palms are affected. The same happens in case of soles.

Keratosis may be mild, moderate and severe. In mild keratosis, small nodules form that can be felt when touched. In moderate keratosis, these nodules grow

and coalesce into wart-like bumps (Figure 3.2). As the nodules thicken, skin can become cracked and vulnerable to secondary infections, leading to debilitation and pain (severe keratosis).

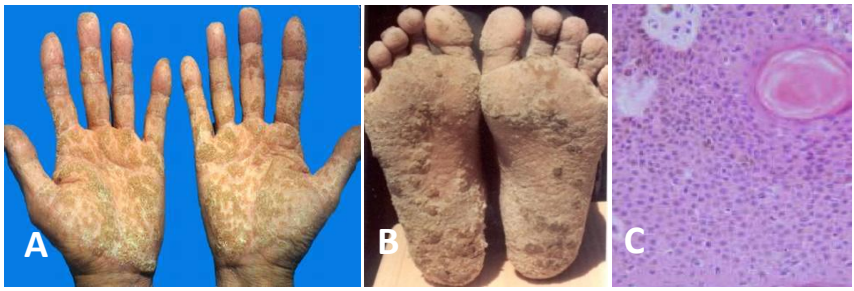

Figure 3.2 *Moderate arsenical keratosis at palms (A), severe form at soles (B) and the histological view (C) (Source: A and B were collected from the internet and C from the reference: An et al., 2004).*

Keratosis develops gradually and the latency period varies greatly. The shortest latency period following ingestion of arsenic contaminated drinking water is 4 years. Most of the multiple keratotic lesions remained for a long time. Only a small portion develops cancer. In a retrospective study of 262 adults treated with Fowler's solution, the minimal latency period for keratosis was 2.5 years, following ingestion of approximately 2.2 g of arsenite (Fierz, 1965).

Palms and soles play important role in transepithelial fluid loss. Arsenic is also excreted through skin including palms and soles. It is not clear whether arsenic or its metabolite is responsible for the development of keratosis.

Skin lesions have been reported even at concentrations below 50 ppb, though this may reflect an incomplete exposure history. Prevalence increases sharply above 300 ppb.

In addition to arsenical keratosis, there may be the other causes: a) actinic keratosis, b) keratosis pilaris, c) seborrheic keratosis, and d) senile keratosis.

Mee's line: Mee's line appears as single, solid, transverse white band of about 1 or 2 mm in width crossing the nail of all fingers at the same relative distance from the base (Figure 3.3). It was first described by R. A. Mees in 1919 in three patients due to homicidal or suicidal arsenic ingestion (Mees, 1919). It should not be confused with Beau's line which is due to growth arrest during bouts of debilitating illness.

In Kurdistan Province (west side of Iran), the prevalence of Mee's line was 86.1% whereas keratosis and melanosis were 77.2% and 67.8% respectively (Barati et al., 2010). Therefore, the prevalence of Mee's line between inhabitants was higher than the other disorders. Mee's line appeared more at arsenic concentrations of 51-200 ppb. Mees' lines are often seen in conjunction with polyneuropathy.

Figure 3.3 *Presence of Mee's line in nail (left); Beau's line (right) is shown for comparison (Source: Internet).*

3.2 Effects on Fetus and Infant

In arsenic endemic areas, human is exposed to arsenic from the beginning of his/her life. It crosses the placenta to the fetus and has impact on pregnancy outcomes. It includes spontaneous abortion, stillbirths, preterm birth rates, low birth weight, and increased infant mortality (Ahmad et al., 2001; Hopenhayn-Rich, 2000). A study on Bangladeshi women of reproductive age

exposed to arsenic contaminated drinking water (>0.05 ppb) for at least five years, there was a significantly greater adverse pregnancy outcome than the non-exposed population (<20 ppb; Ahmad et al., 2001). Another retrospective study of infant mortality in Chile showed a significant association between arsenic exposure and late fetal mortality (*rate ratio* (RR) = 1.7), neonatal mortality (RR = 1.53), and postnatal morality (RR = 1.26) after adjustment for location and calendar time (Hopenhayn-Rich, 2000).

Arsenic is not excreted in breast milk in significant amount. Many women in Matlab, Bangladesh usually do breast-feeding for 12 months or more, however, resulting in limited exposure to child.

3.3 Cardiovascular Diseases

Epidemiological studies have shown a dose-response relationship of arsenic exposure and the development of cardiovascular diseases such as carotid atherosclerosis, hypertension, electrcardigraphic abnormalities (Wang et al., 2007), peripheral vascular disease (blackfoot disease), ischemic heart disease and cerebrovascular disease.

Meta-analysis of 13 studies conducted between January 1966 to April 2005 in general populations (8 in Taiwan, 5 in other countries) and 16 studies conducted in occupational populations were identified (Navas-Acien et al., 2005). In Taiwan, relative risks comparing the highest arsenic exposure category with the lowest ranged from 1.59 to 4.90 for coronary disease, from 1.19 to 2.69 for stroke, and from 1.66 to 4.28 for peripheral arterial disease. In other general populations, relative risks ranged from 0.84 to 1.54 for coronary disease, from 0.69 to 1.53 for stroke, and from 0.61 to 1.58 for peripheral arterial disease. In occupa-tional populations, relative risks ranged from 0.40 to 2.14 for coronary

disease mortality and from 0.30 to 1.33 for stroke mortality.

Even in United States, studies show correlations between standard mortality ratios for cardiovascular diseases and arsenic levels in drinking water (Engel & Smith, 1994; Lewis et al., 1999). Arsenic exposure causes significant increased risk for death in cardiovascular disease-related mortality (Sohel et al., 2009).

Electrocardiography: Electrocardiography shows prolonged QT interval and increased QT dispersion. The prevalence rates of QT prolongation and water arsenic concentrations showed a dose-dependent relationship (p = 0.001). The prevalence rates of QTc prolongation were 3.9, 11.1, 20.6% for low, medium, and high arsenic exposure, respectively (Mumford et al., 2007). QTc prolongation was also associated with sex (females are more susceptible than males) but not age or smoking.

Blackfoot disease: Blackfoot disease is a vascular disease due to chronic ingestion of arsenic. Sporadic cases of blackfoot disease occurred in the beginning of 20th century, but peak incidence was noted between 1956 and 1960, with prevalence rates ranging from 6.51 to 18.85 per 1,000 population in different villages (Tseng, 2005). Blackfoot disease starts with coldness, numbness and pain particularly in feet (Table 3.2). But in rare case, upper extremety is also involved. There is discoloration on the skin. These spots are changed from white to brown and finally to black which are due to loss of circulation (Figure 3.4). Subsequently different degree of ulceration and gangrenous changes are occurred (Figure 3.5). These ultimately lead to severely painful gangrene formation of the extremities (particularly the toes and feet) with spontaneous or artificial amputation of foot. The symptoms of blackfoot disease are similar to those of Burger's disease and

Table 3.2 *Stages of blackfoot disease as classified in Chi-Yi hospital, Taiwan.*

Stage	Symptoms
1	Coldness, numbness and pain
2	Slight ulceration and slight gangrenous changes
3	Definite ulcer and gangrenous changes
4	Gangrenous changes of the affected extremity. Spontaneous or artificial amputation of foot

(Wang et al., 1993)

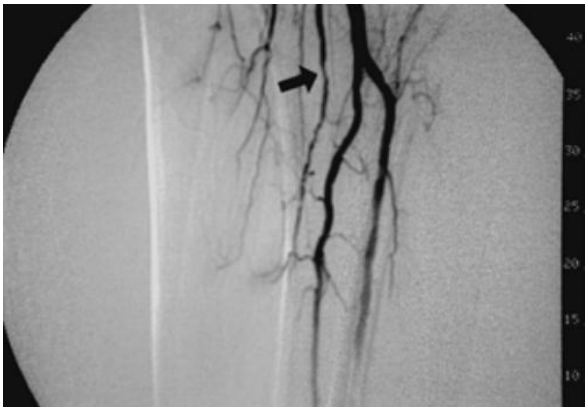

Figure 3.4 *Angiography of patient with blackfoot disease showed prominent occlusion of posterior tibial artery (arrow) with some collateral circulation (Yu et al., 2002).*

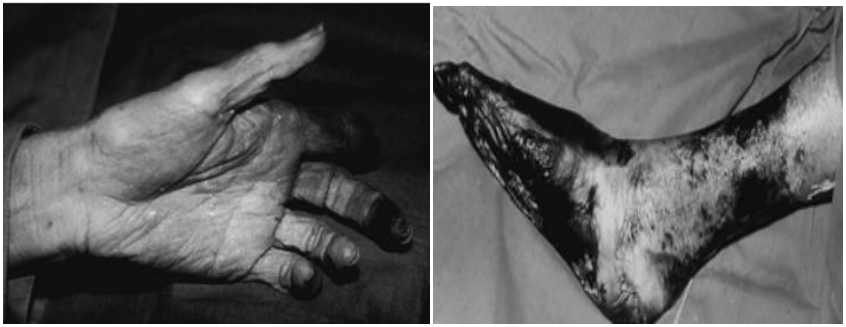

Figure 3.5 *Presence of blackfoot disease resulted in gangrene in hand (left) and leg (right) (Yu et al., 2002).*

thromboangiitis obliterans (Yeh & How, 1963).

The concentrations of arsenic and selenium in hair of patients are significantly higher than those of the controls, but Ca and Zn are significantly lower than those of the controls (Pan et al., 1993). Usually there is a relationship between arsenic and selenium, if there is high concentration of arsenic.

Blackfoot disease has significantly higher mortality rate due to ischemic heart disease (Wu et al., 1989).

The median arsenic levels in artesian wells in Taiwan were ranged from 700 to 930 ppb. Initially it was thought that humic acid in drinking water may be responsible to develop blackfoot disease. The role of humic substances in the development of blackfoot disease is not yet confirmed (Yu et al., 2002).

Hypertension: A meta-analysis on 11 studies was conducted on >20,000 individuals of arsenic exposure and hypertension outcomes, published between 1995 and 2011 (Abhyankar et al., 2012). There was a positive association between elevated arsenic exposure and the prevalence of hypertension, but the implications of this association from a causal perspective are unclear because of the limited number of studies as well as the studies' cross-sectional design, and methodological limitations. Prospective cohort studies in populations exposed to a wide range of arsenic exposure levels, from low through moderate-to-high levels of exposure, are needed to better characterize the relationship between arsenic and hypertension. If the hypertensive effects of arsenic are confirmed, they could partly explain the association between arsenic and cardiovascular disease (Chen et al. 1996; Medrano et al. 2010; Navas-Acien et al. 2005; Wang et al. 2007; Wu et al. 1989).

Given the widespread arsenic exposure through drinking water and foodstuffs, even a modest effect of arsenic on hypertension could have a substantial impact on morbidity and mortality (Kwok, 2007; Manson et al. 1992).

Ischemic heart disease: Increased mortality from ischemic heart disease was first reported in copper smelter workers exposed to arsenic (Lee & Fraumeni, 1969). Epidemiological studies show a correlation between arsenic exposure and a risk of atherosclerosis. It induces endothelial dysfunction, including inflammatory and coagulating activity as well as impairs nitric oxide (NO) balance.

Ischemic heart disease is considered as late clinical manifestations of generalized atherosclerotic process. The risk of atherosclerosis is increased by more than 5-fold in individuals with high plasma homocysteine level (>12.7 mM) and high MMA (>16.5%) concentration in the urine (Wu et al., 2006). Arsenic-related ischemic heart diseases in humans are not associated with serum lipid profiles (Hsueh et al., 1998). Arsenic exposure, through drinking water, was found to increase atheroma formation in apolipoprotein A_/_ mice in parallel with increasing levels of arsenic in the vessel wall. With 100 ppb arsenic exposure, the mortality was 3.5% and nearly doubled to 6.6% with an arsenic exposure of 600 ppb (Chen et al., 1996).

Cerebral infarction: Cerebral infarction is considered as late clinical manifestations of generalized atherosclerotic process. The relative risk for cerebrovascular disease mortality in Taiwan with elevated arsenic drinking water levels in the arsenic-exposed population was 1.14 for males and 1.24 for females per 1,000 (Tsai et al., 1999).

3.4 Endocrine

The relationship between arsenic exposure and diabetes mellitus is observed in people drinking contaminated well water in Taiwan (Lai et al., 1994, Tseng 2004; Tseng et al., 2002) and Bangladesh (Rahman et al., 1998; Rahman et al., 1999),

and in people working in copper smelters (Rahman & Axelson, 1995) and art glass industry (Rahman et al., 1996) in Sweden. A cross-sectional study shows the prevalence rate of diabetes were 2.6, 3.9, and 8.8 with time-weighed average arsenic levels of <500, 500-1000, and >1000 pbb respectively, compared to the control population (Rahman et al., 1998). High chronic exposure to inorganic arsenic in occupational settings was also related to higher levels of glycated hemoglobin, a marker of blood glucose levels (Jensen & Hansen, 1998).

The cause of arsenic-induced diabetes mellitus may be explained in the following way:

Similarity with phosphorus: Inorganic arsenate ($H\mathbf{As}O_4^{2+}$) is a molecular analogue of phosphate (HPO_4^{2+}). Arsenic can compete for phosphate anion transporters and replace phosphate in biochemical reactions (Hughes, 2002). Generation of ATP during oxidative phosphorylation can be inhibited by the replacement of phosphate with arsenate. There is depletion of intracellular ATP by arsenate. The replacement of phosphate in DNA by arsenic is also suggested. Substituting phosphate and forming ADP-arsenate and glucose-6-arsenate, leading to impaired glucose metabolism and inefficient energy production.

High affinity for sulfhydryl groups: Formation of cyclic thioarsenite complex with paired sulfhydryl groups in proteins (insulin, insulin receptor, glucose transporters), and enzymes (pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) could lead to impaired glucose transport and metabolism.

Increased oxidative stress: Oxidative stress can lead to formation of amyloid in pancreatic islet cells, leading to progressive β cell dysfunction. Superoxide may impair insulin secretion by interaction with uncoupling protein 2. Insulin resistance can also be induced by oxidative stress.

Interference with gene expression: Induction of insulin resistance by

enhancing the expression of NF-κB, TNFα, and IL-6 and by inhibiting the expression of PPARγ.

3.5 Respiratory Diseases

Involvement of respiratory diseases includes chronic cough, bronchiectasis and chronic obstructive pulmonary disease (Guo et al., 2007; Guha Mazumder et al., 2005). About 35% patients show chronic cough.

3.6 Liver Diseases

Liver is also involved. There are hepatomegaly (76.6%) and non-cirrhotic portal fibrosis (91.3%) in liver histology (Santra et al., 1999). The maximum arsenic content in liver is reported to about 6 mg/kg. Non-cirrhotic portal fibrosis is the predominant lesion in India (West Bengal). Initial biochemical evidence of hepatic membrane damage, probably due to reduction of glutathione and antioxidant enzymes, may be seen by 6 months. Continued arsenic intake results in fatty liver with serum aminotransferases elevated at 12 months and hepatic fibrosis at 15 months. Liver function test shows elevated globulin levels although the incident is low (6.8%; Guo et al., 2007).

3.7 Nervous System

Neurotoxicity manifestions are loss of hearing 5.9%, loss of taste 5.4%, blurred vision 17.4%, tingling and numbness of the limbs 33.5% and hypertension 8.1% were significantly higher in the arsenic endemic areas (Guo et al., 2007). The most common neurological involvement is the sensory-predominant peripheral neuropathy (Figure 3.6). The mechanism of neuropathy is similar to the

neuropathy of thiamine deficiency (Sexton & Gowdy, 1963). Arsenic inhibits the conversion of pyruvate to acetyl coenzyme A and thereby blocks the Krebs cycle.

Patients may complain of pain and weakness in the extremities, 'pins and needles' in the fingers and toes, difficulty in walking, and other effects (de Wolff and Edelbroek, 1994). Children in Bangladeshi (Wasserman et al., 2004) and Thailand (Siripitayakunkit et al., 1999) exposed to drinking water with arsenic >50 ppb have decreased intelligence testing scores when compare with children exposed to lower levels of arsenic in drinking water.

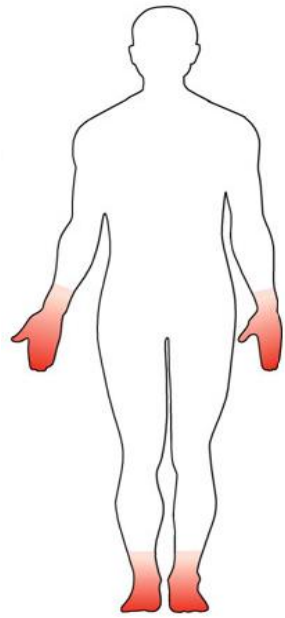

Figure 3.6 *Stocking-glove pattern of peripheral neuropathy (source: internet).*

3.8 Cancer

Since 1980, the International Agency for Research on Cancer (IARC) has considered arsenic as carcinogenic to human. The earliest reports linking

arsenic to cancer involved associations between lung cancer and inhaled arsenic in miners and associations between skin cancer and ingestion of arsenic-based medicines (Bates et al., 1992). An increased prevalence of skin cancer in Taiwanese populations exposed to arsenic in their drinking water was reported in 1968. The populations in most endemic areas, who have been exposed to high levels of arsenic for about 20 years, could have a greatly elevated risk of developing cancer within the next 10 years.

Cancer-death risk associated with daily consumption of 1.6 liters of water with inorganic arsenic (50 pbb) has been estimated to be 21 per 1,000 (Bates at al., 1992).

There is a possibility that because of the latency period for cancer development in human, arsenic-induced malignancies may have not yet peaked in Bangladesh or China. Tsuda et al. (1995) discussed that arsenic exposure level when combined with the presence of skin lesions could be used to estimate the future development of malignancy.

Arsenic exposure causes significant increase in the risk for death in cancer-related mortality. A clear dose-response relationship was observed (Sohel et al., 2009).

3.8.1 Skin Cancer

Arsenic-induced skin cancer includes Bowen's disease, squamous cell carcinoma and basal cell carcinoma. Squamous cell carcinoma and basal cell carcinoma are usually referred to as nonmelanoma skin cancer. This has a major cause of morbidity but has low fatality case. Figure 3.7 shows the skin layer from which squamous cell carcinoma and basal cell carcinoma are originated.

Bowen's disease: It was named after an American dermatologist John

Templeton Bowen (1857-1940). Bowen's disease usually appears as a persistent reddened scaly patch on the skin that is 1-3 cm in diameter and which may or may not be itchy. The affected skin can be red and sore and may bleed and scab (Figure 3.8). Bowen's disease typically presents as a gradually enlarging, well-demarcated erythematous plaque with an irregular border and surface crusting or scaling. Bowen's disease usually occurs as a solitary lesion, but the number may be several. Although Bowen's disease may resemble a superficial basal cell epithelioma, it differs by not showing a fine pearly border.

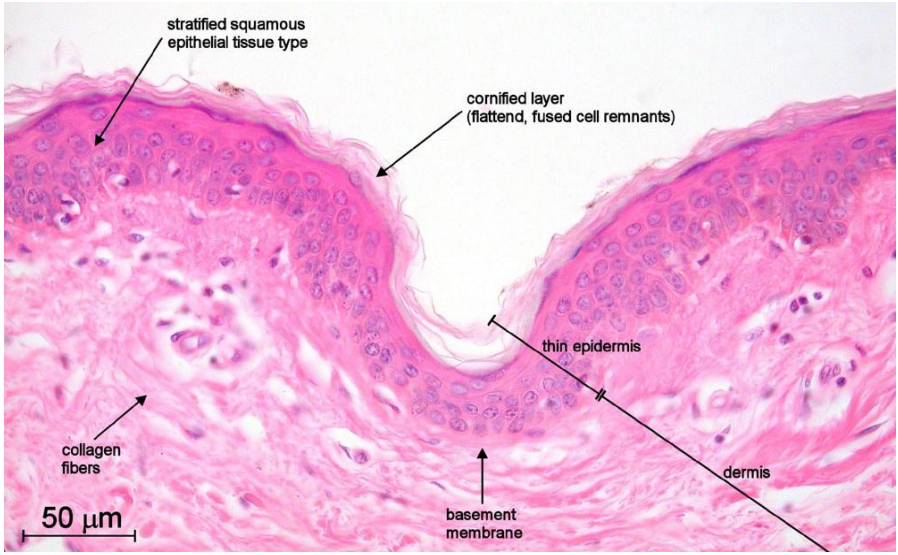

Figure 3.7 *Cross-section of the normal skin shown under microscope. Squamous cell carcinoma arises from the stratified squamous epithelial cells whereas basal cell carcinoma arises from the basal layer of keratinocytes (source: internet).*

Bowen's disease may develop in exposed or non-exposed areas. When it occurs in exposed areas, it is usually due to solar keratosis. When it occurs in non-exposed areas, it may be due to arsenical keratosis.

This disease is sometimes referred to as 'squamous cell carcinoma *in situ*', as the cancerous cells are contained in this top layer. Bowen's disease has a risk

(3-5%) to develop invasive squamous cell carcinoma (Neubert & Lehmann, 2008).

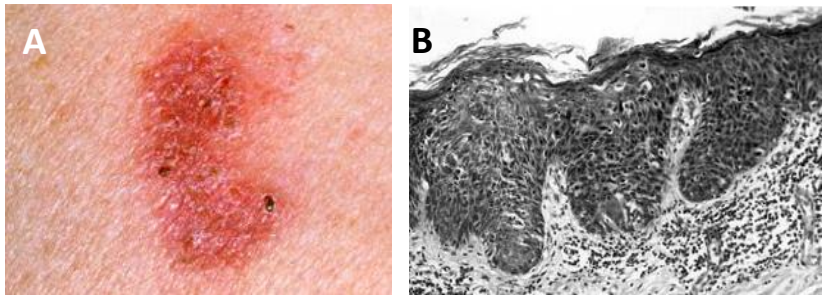

Figure 3.8 *Bowen's disease in skin due to chronic consumption of arsenic (A) and its histological appearance (B). The figure A is from the internet and the B from the reference: Centeno et al., 2002.*

Arsenic-related Bowen's disease can appear 10 years after arsenic exposure, while other types of skin cancer can have a latency period of 20 or 30 years (Yoshida et al., 2004).

Bowen's disease may occur at any age in adults, but is rare before the age of 30 years. Most of the patients are aged over 60.

The most characteristic changes are intact basement membrane; widened intercellular spaces with microvillus-like cytoplasmic projections; a decrease in intercellular desmosomes; many dyskeratotic epithelial cells; many normal and abnormal mitotic figures; the presence of giant cells; numerous intracytoplasmic desmosomes; and vacuolar degeneration of keratinocytes (Yeh et al., 1974).

There are atypical and pleomorphic keratinocytes with scattered mitotic figures are present at all levels of the hyperplastic epidermis.

Bowen's disease is not only due to arsenic but also due to solar damage, *immunosuppression* (including AIDS), viral infection (human papillomavirus or HPV), chronic skin injury, and other *dermatoses*.

Squamous cell carcinoma: Squamous cell carcinoma is a true invasive carcinoma of the surface epidermis, consisting of irregular masses of epidermal cells that proliferate downward and invade the dermis. The dermis shows a moderate inflammatory reaction (Figure 3.9 and Figure 3.10). It is the most common form of skin cancer.

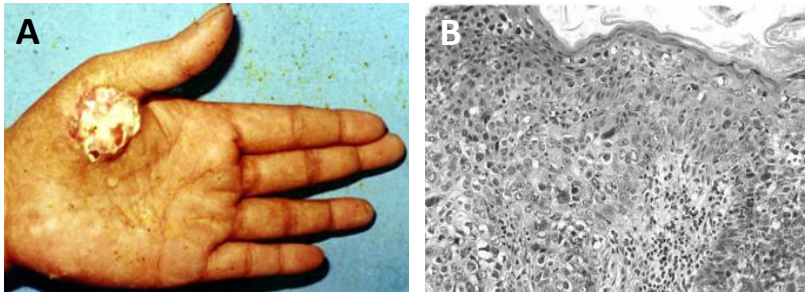

Figure 3.9 *Squamous cell carcinoma in hand due to chronic consumption of arsenic (A) and its histological appearance (B). A is taken from the internet (Courtesy from Arsenic Foundation) and B is taken from the reference: Centeno et al., 2002.*

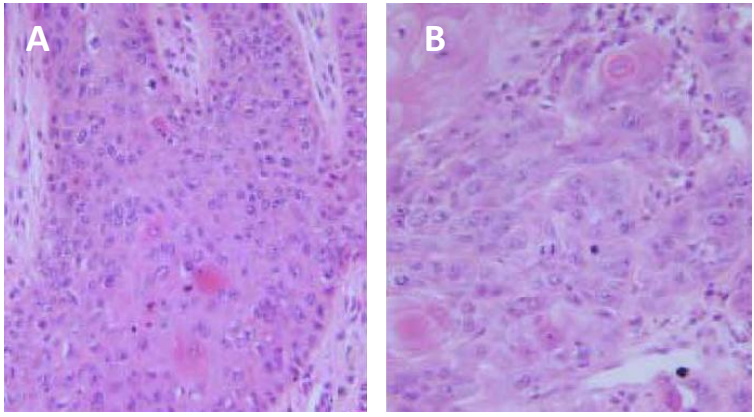

Figure 3.10 *Histological appearance of squamous cell carcinoma due to chronic consumption of arsenic (A) and non-arsenic related (B) (Centeno et al., 2002).*

Basal cell carcinoma: Basal cell carcinoma is composed of cells similar to those found in the basal areas of the epidermis and appendages. It is slow growing skin tumor. Early basal cell carcinoma is translucent or pearly, with

raised, rounded areas covered by thin epidermis through which dilated vessels may show (Figure 3.11). Occasionally pigment can be seen. They have a large, oval or elongated nucleus with relatively little and poorly defined cytoplasm. There are elongations of the epidermis downward into the dermis with nuclear palisading of the peripheral cell layer (shown by arrow; Figure 3.11C).

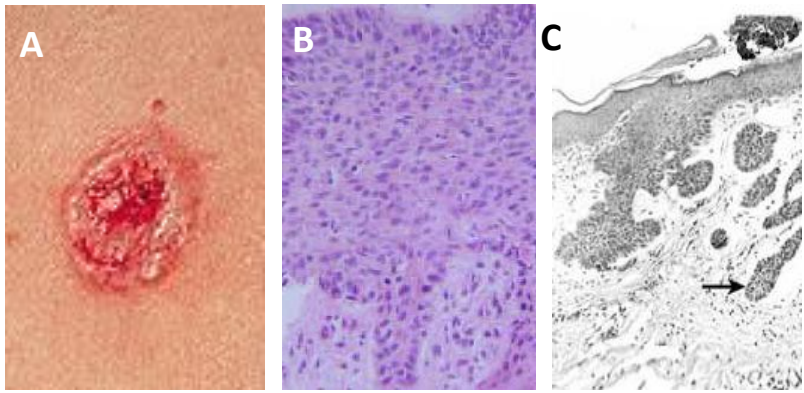

Figure 3.11 *Basal cell carcinoma in skin due to chronic consumption of arsenic (A) and its histological appearance (B: Centeno et al., 2002) and (C): An et al., 2004).*

3.8.2 Lung Cancer

Drinking water: Lung cancer has proven to be amongst the most deadly cancer types following arsenic exposure (Smith et al., 1992). Lung adenocarcinoma is the most common type of lung cancer worldwide, however, the most frequent histological subtypes observed in arsenic-induced lung tumors among both smokers and non-smokers are squamous cell carcinomas and small cell carcinomas. Lung tumors derived from individuals exposed to arsenic also exhibit differential genetic and epigenetic changes when compared to histologically matched tumors derived from an arsenic-free environment. The differential molecular alterations seen in arsenic-induced tumors may not arise from inorganic arsenic, but instead from more damaging arsenic species generated through its metabolism (Barrett et al., 1989).

The association between arsenic in drinking water and lung cancer was first observed in southwestern Taiwan, where blackfoot disease is endemic (Chen et al. 1962).

A systematic review of the articles published through April 2006 (nine ecological studies, two case-control studies, and six cohort studies) were conducted in areas of high arsenic exposure (100 ppb) in Taiwan, Japan, and Chile. Most of the studies reported markedly higher risks of lung cancer mortality or incidence in high arsenic areas compared to the general population or a low arsenic exposed reference group. The quality assessment showed that, among the studies identified, only four assessed arsenic exposure at the individual level. Further, only one of the ecological studies presented results adjusted for potential confounders other than age; of the cohort and case-control studies, only one-half adjusted for cigarette smoking status in the analysis. Despite these methodologic limitations, the consistent observation of strong, statistically significant associations from different study designs carried out in different regions provide support for a causal association between ingesting drinking water with high concentrations of arsenic and lung cancer. The lung cancer risk at lower exposure concentrations remains uncertain.

Occupational exposure: Occupational exposure to inorganic arsenic (among miner) through the inhalation of dust particles is associated with an increased risk of developing lung cancer (Lundstrom et al., 2006; Chen & Chen, 2002; Lubin et al., 2000; Jarup & Pershagen, 1991; Enterline et al., 1987). A study on 2,802 men who worked 1 year or more during the period of 1940-1967 at a copper smelter in Tacoma, Washington, found that men with a cumulative air arsenic exposure of ≥45,000 μg arsenic/m^3-years had a respiratory cancer SMR of 338.5 compared to the general population (Enterline et al. 1987). A cohort on 8346 tin miners in Yunnan, China, reported that exposures of ≥16,093 μg arsenic/m^3 per month was

associated with an approximate 4-fold increase in lung cancer risk compared to exposures of 0.062-1.731 μg arsenic/m^3 per month (Qiao et al., 1997). In both cohort and case-control studies, a consistent dose-response pattern has been observed between cumulative arsenic exposure and lung cancer risk. In contrast to the drinking water studies which suggest a linear dose-response relationship between arsenic exposure and lung cancer mortality, the occupational studies indicate a supralinear dose-response relationship (Hertz-Picciotto & Smith, 1993). Arsenic particles in lungs have low solubility and are, therefore, less rapidly eliminated from the body (Tapio & Grosche, 2006). Using electron-probe microanalysis, Liu and Chen (1996) showed that the content of arsenic in the lung is 17 times higher among patients diagnosed with lung cancer compared to unexposed, disease-free individuals. Inhaled arsenic may cause lung cancer in part through mechanical inhalation, contributing to inflammation of the lung tissue (Tapio & Grosche, 2006). Inhaled arsenic may also contribute to lung carcinogenesis through mechanisms similar to ingested arsenic, including oxidative stress, increases in cellular proliferation, altered DNA repair, altered DNA methylation patterns, and suppression of p53 (Kitchin, 2001; Tapio & Grosche, 2006). Evidence from studies of occupational exposure supports the principle that arsenic acts as a lung carcinogen.

The mechanistic pathways through which exposure to arsenic via the respiratory route in occupational settings cause lung cancer likely differs from the pathways through which arsenic ingested via drinking water causes lung cancer.

3.8.3 Kidney Cancer

The lifetime risk of kidney cancer of men exposed to inorganic arsenic at a dose of 1 μg/kg body weight/day was 0.42%, and that of women was 0.48% (Chen and Wang, 1990). That is, males are equally affected as females.

Long-term exposure to arsenic trioxide can cause chronic kidney damage with abnormal levels of urinary proteins, higher levels of serum non-protein nitrogen, and elevated levels of urinary arsenic.

3.8.4 Liver Cancer

Two types of liver cancer have been associated with arsenic exposure: hepatocellular carcinoma and angiosarcoma of the liver.

Hepatocellular carcinomas: Histologically, hepatocellular carcinomas range from well differentiated to quite anaplastic undifferentiated lesions (Centeno et al., 2002). In the moderately to well-differentiated types, trabeculae are more than two or three cells thick and are composed of tumor cells that exhibit round to oval nuclei with a high nuclear/cytoplasmic ratio and prominent nucleoli. The nuclei are irregular, hyperchrmatic and occasionally multi-nucleated (Figure 3.12). They are surrounded by sinusoidal spaces. The malignant cells often have an abundant eosinophilic cytoplasm and may contain bile, fat, glycogen, or cytoplasmic inclusions. In addition, other clues helpful in diagnosis are the presence of mitoses, tumor within vascular structures, and infiltration of tumor into adjacent liver.

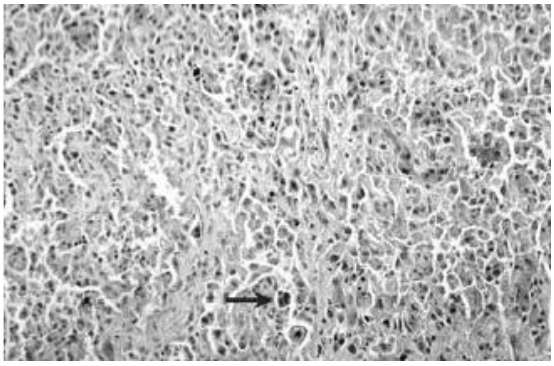

Figure 3.12 *Histological view of hepatocellular carcinoma. The nuclei are irregular, hyperchromatic, and occasionally multinucleated (see arrow).*

Angiosarcoma of the liver: Tumor cells show marked pleomorphism and nuclear hyperchromasia (see arrow; Figure 3.13)

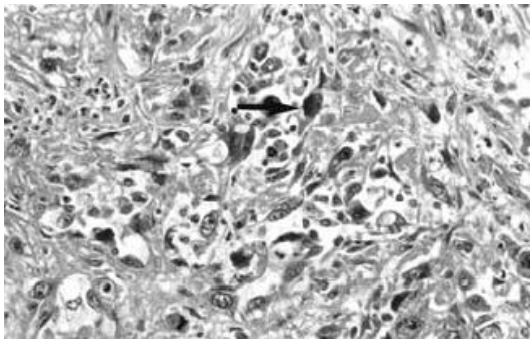

Figure 3.13 *Histological view of angiosarcoma of the liver.*

A significant reduction in the phytohemagglutinin-induce proliferative response of lymphocytes from subjects chronically exposed to arsenic via drinking water (390 ppb; Ostrosky-Wegman et al., 1991). Chronic arsenic exposure alters human immune function. A positive response to HPV increased the OR for non-melanoma skin cancer and that the combination of exposure to high levels of arsenic and a positive response to HPV further increased non-melanoma skin cancer risk (Rosales-Castillo et al., 2004).

Chronic exposures to water contaminated with low concentrations of arsenic do not, however, show the same strong associations with increased cancer incidence and mortality. For example, a study carried out in Denmark (Baastrup et al., 2008) did not find any significant association between exposure to low concentrations of arsenic in drinking water (0.05-25.3 ppb) and risk of melanoma or lung cancer, among other types of neoplasias. Similarly, another study conducted in Belgium did not find a significant correlation between exposure to drinking water containing relatively low arsenic concentrations (20-50 ppb) and lung cancer mortality (Buchet et al., 1998).

3.9 Questions to be Raised

1. Melanosis and keratosis are the earliest symptoms of arsenicosis. Why does melanosis occur earlier than keratosis?

2. Why does melanosis appear in the unexposed part of the body skin instead of throughout the whole body? Arsenic and its metabolites are excreted through skin and accumulated in the cloths. Is there any role of accumulated arsenic and metabolites on the changes in skin?

3. Why both palms or soles are affected by keratoses in arsenicosis?

4. Why does keratosis not present in the skin other than palm or sole of Bangladeshi or Indian patient?

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✶ Myth 1

Arsenical keratosis is nothing but leprosy.

Chapter

4

〖Biomarkers of Arsenicosis〗

A biomarker is defined as a xenobiotically induced alteration in cellular or biochemical components or processes, structures or functions, which is measurable in a biological system or sample (Marchiset-Ferlay et al., 2012). The selection of biomarker depends on reliability, less invasive sample as well easy to obtain are considered.

Diagnosis of arsenicosis is a difficult one. Traditionally it is based on the history of arsenic exposure, clinical feature(s), and presence of arsenic in hair, nail, or urine. If the patient is from an arsenic endemic area and has clinical feature of non-malignant skin manifestations, then it is easy to diagnosis it. On the other hand, a diabetic patient with arsenic in urine is difficult to establish it as a case of arsenicosis. We will face this problem until a biomarker specific for arsenicosis is identified.

Other biomarkers for arsenicosis such as micronuclei, sister chromatid exchange and HPRT mutant frequency have been described but they are not specific for arsenicosis (Table 4.1). Serum CC16 shows promise as a biomarker for assessing early respiratory damage induced by arsenic. There is an association between As^{III} methyltransferase polymorphism and arsenic-induced skin lesions (Valenzuela et al., 2009).

Table 4.1 *Possible biomarkers of arsenicosis.*

Sample	Biomarker
Hair	Arsenic
Nail	Arsenic
Blood	Malondialdehyde, metallothionein, micronuclei, sister chromatid exchange, HPRT mutant frequency, thioredoxin1, CC16, arsenic
Urine	Arsenic, malondialdehyde, 8-hydroxy-2'-deoxyguanosine, N-acetyl-β-D-glucosaminidase, microalbumin, retinol binding protein, β_2-microglobulin, transferring, porphyrin, coproporphyrin-III
Oral mucosa cell	Micronuclei
Urothelial cell	Micronuclei

Scalp hair: Hair is rich in α-keratin that contains abundant cysteine residues (10-14%) to which arsenic binds and thereby accumulates arsenic. The concentration of arsenic in the scalp hair of normal individual is in the range of 0.02-0.2 μg/g of hair (Valentine et al., 1979; Olguin et al., 1983). Arsenic deposition in hair begins within 2 weeks of exposure and remains in these tissues for the next 1-2 years of life (Madorsky, 1977).

Arsenic exposure must be considered when its level is >0.5 μg/g of hair. This concentration of arsenic in arsenicosis is increased up to 10 μg/g of hair (Das et al., 1995). Presence of high concentration of arsenic in hair indicates recent or past exposure to arsenic. The arsenic level in hair of the patients of blackfoot disease is significantly higher than that of the controls, but still below the critical value of 1 μg/g (Lin &Yang, 1988). Sometimes the normal value of arsenic in hair does not exclude the diagnosis. Animal experiments have shown

that ingested organic arsenic (arsenobetaine and arsenocholine) is not deposited in hair (Vahter et al., 1983).

Speciation of arsenic is also examined. Scalp hair mainly contains As^{III} (60.9%) and As^{V} (33.2%). Others are MMA^{V} (2.2%) and DMA^{V} (3.6%), but no DMA^{III} (Mandal et al., 2003). No organic arsenic is accumulated in the hair following ingestion of fish arsenic.

Advantages – The use of scalp hair is a non-invasive method, easy to collect the sample and transport it from the field to the laboratory without any preservative.

Disadvantages – External contamination of arsenic is an important factor. When a person washes his/her hair with arsenic contaminated water without drinking shows high concentration of arsenic in hair (Harrington et al., 1978). There may lead to false positive result. Some patients do not prefer to give the sample due to superstition. Patient looks odd after proper collection of hair from the head so that the patient has to remove either all the hair after giving the sample or wear a cap on the head. In case of male patient, it may be done but in female, it is difficult to perform.

Nail: Like scalp hair, fingernail or toenail is rich in α-keratin that contains abundant cysteine residues (up to 22%). The concentration of arsenic in the nail of normal individual is 0.02-0.5 μg/g. Like scalp hair, arsenic deposition in nail begins within 2 weeks of exposure and remains in these tissues for the next 1-2 years of life (Madorsky, 1977). Arsenicosis must be considered when its level is >1.0 μg/g of nail which is double the value of scalp hair. Presence of high concentration of arsenic in nail indicates recent or past exposure to arsenic. Like scalp hair, the normal value of arsenic in nail does not exclude the diagnosis.

Fingernail contains As^{III} (58.6%), As^{V} (21.5%), MMA^{V} (7.7%), DMA^{III}

(9.2%), and DMA^V (3.0%) (Mandal et al., 2003).

Advantages – The advantage of using nail is its slow growth rate, high affinity of arsenic for keratin, relatively easy to collection, storage and transport to the laboratory from the field without any preservative. It is a non-invasive method and is more preferable than scalp hair due to comperatively less chance of external contamination with arsenic. Toenail is more preferable than fingernail due to comparatively less chance of external contamination. Normal level of arsenic is a bit higher that is helpful for the less sensitive method of estimation. Unlike hair, there is no superstition of giving nail sample by the patient.

Disadvantages – External contamination of arsenic may cause false positive result. Time is needed to grow the nail, particularly toenail in order to collect it.

Urine: The normal level of total arsenic in blood is <1 μg/L in an un-exposed person. Urine is used not only for estination of total arsenic but also for speciation. The presence of arsenic in urine indicates recent exposure of arsenic. Patients of blackfoot disease not only excrete arsenic in their urine but also mercury and lead. However, the urinary zinc and selenium are significantly lower in blackfoot diease than those of the normal controls (Horng & Lin, 1997; Lin &Yang, 1988).

Advantages – It is a non-invasive method and easy to collect. High concentration of arsenic in urine is useful for monitoring ongoing exposure.

Disadvantages – Special precaution is necessary for transport from the field level to the laboratory. There is lack of uniformity in sampling. 24-hours urine collection is sometimes difficult when the sample size is large. The main drawback with spot urine sample is the variation in dilution due to differences in the state of hydration, linked to fluid intake, physical activity and atmos-

pheric temperature (Marchiset-Ferlay, 2012). That is why, spot urine may not give the true result. Several confounding factors like age, sex, diet may influence the conclusion. For example, presence of arsenic of fish origin must be excluded if the urine level is used to identify possible toxicity (Hindmarsh, 2002). Fasting condition also affects the level of arsenic in urine. The percentage of urinary MMA level is found to be significantly increased after fasting (Brima et al., 2007). The time elapsed between the collection of urine and its analysis for arsenic is also important for correct estimation.

Blood: The normal level of total arsenic in blood is <1 μg/L in unexposed person. It is used not only for the estination of total arsenic, but also for speciation, malondiadehyde, metallothionein, micronuclei, sister chromatid exchange, HPRT mutant frequency, thioredoxin1 and CC16 levels. Patients of blackfoot disease showed significantly lower concentrations of selenium and zinc in the blood than the normal control (Lin &Yang, 1988). The amount of arsenic in blackfoot disease is about 60 ppb. It is present more in the red blood cell (98 ppb) than in plasma (38 ppb) (Heydorn, 1970).

Very low amount of arsenic is present in blood in individual even exposed to high concentration of arsenic.

Advantages – Blood arsenic is typically used as an indicator only in the case of very recent exposure or relatively high-level exposure following acute arsenic poisoning.

Disadvantages – It is an invasive method. However, low-level of inorganic arsenic exposure from drinking water and organic arsenic from food are difficult to distinguish, thus causing a limitation of blood arsenic levels as indicators (NRC, 1999). Therefore, a more sensitive method of estimation is required.

Micronuclei: The formation of micronucleus is one of the most sensitive biomarkers of chromosomal damage and genome stability in human populations (Figure 4.1) (Moore et al., 1997). The frequency of micronuclei in the arsenic exposed people is significantly elevated to 5.33-fold over unexposed levels for lymphocytes, 4.63-fold for oral mucosa cells, and 4.71-fold for urothelial cells (Basu et al., 2004). Among these three cell types, slightly higher level of micronuclei being observed in lymphocytes compared with oral mucosa and urothelial cells.

Usefulness of micronuclei assay as a screening and early detection technique for cancer susceptibility has been suggested. The normal mammalian cell culture derived from male Chinese hamster lung fibroblast cells (V79) was used as the test system to assess the genotoxicity by micronucleus assay. The results showed that both green tea and black tea extracts have equal potentiality in modulating the arsenic-induced genotoxicity (Sinha et al., 2005).

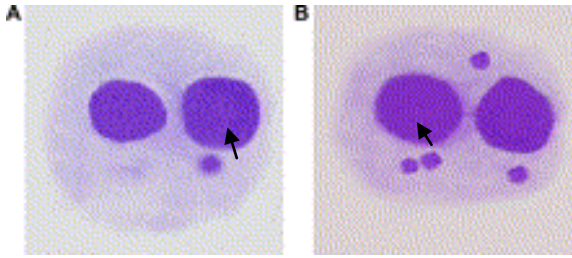

Figure 4.1 *Representative images of micronuclei formation (arrow) in erythrocytes of Tilapia fish after exposure to arsenic ($NaAsO_2$) for 96 hours; (A) moderate micronucleus formation at 3 ppm and (B) severe micronucleus formation at 56 ppm of exposure respectively.*

Several confounding factors like lifestyle (exercising, drinking, and smoking), dietary (folate deficiency, plasma levels of vitamin B_{12} and homocysteine) and demographic factors (age and gender) can influence the formation and the frequency of cellular micronuclei (Ishikawa et al., 2003).

Sweat: The skin of healthy control secretes very low amount of arsenic (mean ± SE; unit: μg/inch^2 of skin/24 hours; chest: 0.6 ± 0.2: back: 0.3 ± 0.1; and abdomen: 0.5 ± 0.2) (Yousuf et al., 2011). Several folds higher amount of arsenic is secreted in people exposed to arsenic. Highest amount is found in the chest for arsenic-exposed controls (8.4 ± 1.8) and patients (9.2 ± 1.3), respectively). The lowest amount is secreted in the abdomen of arsenic-exposed control (6.5 ± 1.7) and patient (5.2 ± 1.0), respectively). No significant differences are observed between the arsenic-exposed control and patient in arsenic secretion through skin.

E. coli in stool: Arsenic exposure decreased the colony count of *E. coli* in stool. It is severely reduced in the stool of patients. In addition, excretion of arsenic in the stool of arsenic exposed control and patient is increased. However, patients show less excretion of *E. coli* in stool than arsenic exposed controls (Rashid et al., 2014).

Sister chromatid exchange: Sister chromatid exchange means the exchange of genetic materials between the two identical sister chromatids. Four to five sister chromatid exchange per chromosome pair per mitosis is in the normal distribution. Frequent sister chromatid exchange may also be related to the formation of tumor. As^{III} induces a significantly increased frequency of sister chromatid exchange in Chinese hamster and Syrian hamster embryo cells. As^{V} is one order of magnitude less potent in inducing sister chromatid exchange than As^{III}.

Hypoxanthine guanine phosphoribosyltransferase (HPRT) gene: HPRT is an enzyme encoded in humans by the HPRT1 gene. It catalyzes the conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate. HPRT gene is located on the X chromosome. Study was conducted to investigate the feasibility of using mutagenesis of the hypoxanthine guanine

phosphoribosyl transferase (HPRT) gene in T-lymphocytes as a quantitative biomarker for detection of biological damage caused by arsenic (Harrington-Brock et al., 1999). The HPRT T-cell assay does not appear to have sufficient sensitivity to be useful as a biomarker of genetic effects caused by low-level arsenic exposure.

Metallothionein: Metallothionein is a low molecular weight (500 to 14,000 Da) metal-binding protein that protects our body against metal intoxication. It is rich in cysteine. Blood metallothionine level is significantly lower in arsenicosis in Guizhou as compared to control (Liu et al., 2007). Metallothionein has the capacity to bind zinc, copper, selenium, cadmium, mercury, silver, arsenic through the thiol group of its cysteine residues. So, metallothionein level is not specific for arsenicosis.

Porphyrin: The well-known porphyrin is the heme. Coproporphyrin is the metabolite arising from heme synthesis. The major abnormalities in the urinary porphyrin excretion pattern observed in arsenic-exposed individuals are: a) significant reductions in coproporphyrin III excretion resulting in decrease and b) significant increase in uroporphyrin excretion (Garc á-Vargas et al., 1994). Both alterations are responsible for the decrease in the COPRO/URO ratio. No porphyrinogenic response is found in individuals with urinary arsenic concentrations (<1,000 μg arsenic/g creatinine). A study in the Guizhou Province, China, found significantly raised levels of urinary uroporphyrin-III and coproporphyrin-III (but not coproporphyrin-I) in the arsenic-exposed group as compared to control (Deng et al, 2007).

Malondiadehyde: The level of malondialdehyde in plasma, erythrocyte or urine may be used as a biomarker of oxidative stress. The level of urinary malondiadehyde in arsenicosis (arsenic contaminated by coal burn) is increased which indicates that arsenic exposure causes oxidative stress (Wang et al.,

2009). This biomarker is not specific for arsenic.

Reduced glutathione: Arsenicosis shows low level of reduced glutathione (GSH). The mean GSH level in red blood cells in arsenicosis is 55.3 mg/dL, in arsenic exposed family members is 57.8 mg/dL, and in the normal control group is 88.7 mg/dL (Sinha et al., 2003).

8-Hydroxy-2'-deoxyguanosine (8-OHdG)**:** The oxidative damage permanently occurs to lipids of cellular membranes, proteins, and DNA. In nuclear and mitochondrial DNA, 8-OHdG is one of the predominant forms of free radical-induced oxidative lesions, and has, therefore, been widely used as a biomarker for oxidative stress and carcinogenesis. Urinary 8-OHdG shows a significant dose-response relationship after 8 months of exposure of arsenic. This marker is also not specific.

Studies were done to find out an effective biomarker of kidney toxicity caused by exposure to arsenic. These studies are focused on N-acetyl-β-D-glucosaminidase, β_2-microglobulin, microalbumin and retinol binding protein (Buchet et al., 2003).

Microalbumin: α1-Microglobulin is one of the three original members (α1-microglobulin, retinol binding protein and β-lactoglobulin) of the lipocalin superfamily. Its function in blood and urine is not clear. However, it may play a biological role as an anti-oxidant with oxidant-scavenging and enzymatic reductase properties. α_1-Microglobulin in medium and severe form of arsenicosis is significantly higher than that in the control group (Zhang et al., 2006).

Retinol binding protein: Retinol binding protein, a carrier protein of retinol, has diverse functions. Urinary retinol binding protein is the sensitive indicator of renal tubular damage. This protein is significantly higher in medium and severe form of arsenicosis than that in the control group (Zhang et al., 2006).

Transferrin: Transferrin (80,000 Da) is an iron binding protein in the blood that transports iron throughout the body. Its level rises in case of iron deficiency and fall in cases of iron overload. Transferrin level in severe arsenicosis is increased significantly compared with the control group (Zhang et al., 2006).

Heme oxygenase: Physiological degradation of heme to biliverdin is mediated by an enzyme heme oxygenase (31,000 Da). This enzyme is present within the macrophage. Biliverdin is converted to bilirubin by biliverdin reductase. Bilirubin is then enter into the intestine through bile duct. Bilirubin is converted to urobilinogen (stercobilinogen) by removing glucuronic acid by bacteria within the intestine (Figure 4.2). Some amount of urobilinogen is converted to stercobilin and others enter into the liver via portal vein (enterohepatic circulation).

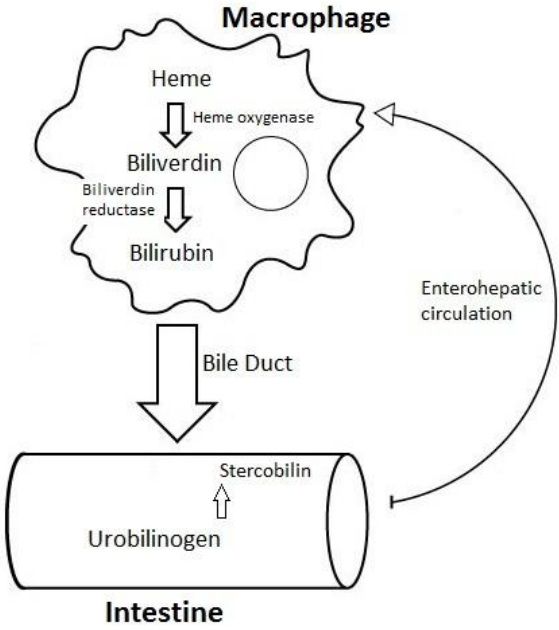

Figure 4.2 *Role of heme oxygenase in heme metabolism.*

The activity of heme oxygenase is increased up to 100-fold by a wide variety

of stimuli (metals, heme and hormones). It is also increased in arsenicosis which may be due to arsenic (Del Razo et al., 2001). Therefore, induction of heme oxygenase is not specific for arsenicosis.

Thioredoxin: Thioredoxin is a protein (12,000 Da) that acts as an antioxidant by facilitating the reduction of other proteins by cysteine thiol-disulfide exchange. There is a significant increase in the concentrations of serum thioredoxin1 in low, medium, high arsenic exposure groups, and the arsenicosis group, in a dose-response manner (Li et al., 2012). Thioredoxin might play an important role in the methylation of arsenic by the enzyme arsenic III methyltransferase due to the fact that serum thioredoxin1 level appears to be necessary for the catalysis of arsenic methylation (Thomas et al., 2004; Waters et al., 2004).

4.1 Collection of Sample

Water: Study participant is provided with acid-washed (nitric acid-water, 1:1) plastic bottle (50 mL size) for the collection of drinking water sample into which nitric acid (1.0 mL/L or 1 drop/50 mL bottle) is added later on as a preservative.

Blood: Whole blood, serum, plasma and erythrocytes are collected from the venous blood.

Urine: First morning void is collected in precoded polypropylene bottle (50 mL size) for arsenic estimation as this gives the best measure of recent arsenic exposure. Immediately after collection, the sample is stored and carries to the laboratory at 0 ℃ at ice box and then is kept at – 20 ℃ until estimation is carried out. Concentrated HCl (1 mL/100 mL urine) is added in the urine sample to prevent bacterial growth. Urine sample should be filtered before analysis in

order to remove epithelial cells that may contain arsenic. This will help to get the exact result of the amount of arsenic in urine.

Nail: Ceramic blade cutter is used to collect nail sample. Use of normal blade may increase the amount of arsenic in nail. After collection, the sample is thoroughly cleaned by sonication with double distilled water followed by an acetone wash for 5 min to remove exogenous arsenic.

Hair: Ceramic blade cutter is used to collect scalp hair sample. Usual scissors is avoided for external contamination of arsenic. Sample is thoroughly cleaned like nail to remove exogenous arsenic. Hair sample is of similar size and is taken from more or less similar region of head (close to the scalp behind the ear with a diameter of about 1 cm) (Maki-Paakkanen et al., 1998). The selection of this area is due to less chance of external contamination. Another option is to collect hair sample of at least 1 g of hair from several sites on the head and a mean level should be taken (Hindmarsh, 2002).

Oral mucosa cell: Oral mucosa cell sample is collected from each subject using a soft toothbrush to scrape cells gently from the oral mucosa (inside of both cheeks). The brush is then swirled into a centrifuge tube containing a buffer solution containing EDTA (0.1 M), Tris-HCl (0.01 M), NaCl (0.02 M; pH 7.0) (Warner et al., 1994), thereby creating a cell suspension. The cell suspension is stored at 2-4 ℃ in a cooling device and brought to the laboratory within 2 hours of sample collection.

Urothelial cell: To collect urothelial-exfoliated cells, each subject is asked to provide 50 mL of the urine sample from the second and third voids of the day. The urine sample is coded, kept at 2-4 ℃ in a cooling device, and carries to the laboratory within 2 hours of sample collection. First morning void is not used for micronuclei assay because exfoliated cells tend to degrade from overnight

exposure to urine. Female generally exfoliates more cells per void than male.

4.2 Laboratory Analysis

Hair: Hair sample is used for the estimation of total arsenic or speciation. Estimation of total arsenic is usually done and requires less expensive equipment. Speciation of arsenic in hair is carried out by HPLC-ICP-MS. For each case, hair sample is digested with acids at 90 ℃ until the white fume comes out.

Nail: Estimation of arsenic in nail is similar to hair.

Micronuclei assay in exfoliated epithelial cells: Oral mucosa cells are obtained by simply centrifuging the cell suspension at 1,500 rpm for 10 min. The supernatant is discarded and cell pellets are resuspended in fresh buffer solution. Cells are washed thrice with the buffer solution. Gentle pipetting of cells in the buffer solution reduces clumping and lyse broken cells. Volumes of 25 mL of the buffer solution in 50 mL conical tubes are used in every washing step.

Urothelial cells: Urothelial cells are recovered by centrifuging urine samples (2,000 rpm for 15 min) and washing the cell pellet with 0.9% NaCl. Cell suspension of both cell types (50 μL) is laid and spread well on clean, preheated (40 ℃) glass slides and allows to air-dry for 5-10 min. Cell density is checked with a phase-contrast microscope. The cell solution is either concentrated by centrifugation or diluted in the buffer solution (for oral mucosa cells) or 0.9% NaCl (for urothelial cells) as required. Once the desired cell density (no overlapping cells) is reached, more slides are prepared. The slides are fixed in methanol (80% v/v) at 0 ℃ for 20 min and air-dried.

Micronuclei in oral mucosa cells are scored in accordance with the criteria reported (Tolbert et al. 1992), while urothelial cells are analyzed by the method

described (Reali et al. 1987). At least 3,000 oral mucosa cells and 1,000 urothelial cells are scored per individual.

Micronuclei assay in lymphocytes: Lymphocyte cultures are carried out for micronuclei analysis following the protocol (Fenech, 1998). The whole blood cultures are incubated for 44 hours at 37 ℃. Cytochalasin B is added to each culture to give a final concentration of 6 μg/mL and the culture is incubated at 37 ℃ for an additional 28 hours to induce binucleated cell formation. After a total of 72 hours incubation, the cells are centrifuged at 1,000 rpm for 5 min. Supernatant is discarded and cell pellets are treated with 0.075 M KCl/saline (1:9) for 5 min. After centrifugation, the cells are fixed in fresh fixative (methanol/glacial acetic acid, 3:1). Fixative is removed by centrifugation and two more changes of fixative are performed. The cells are dropped onto wet clean slides and the slides are air-dried and stained with 5%Giemsa in phosphate buffer (pH 6.8). Finally binucleated cells from each subject are examined for micronuclei under the microscope.

Scoring procedure – All slides are first examined with low-power (20x) magnification using a compound microscope to discard those infected with bacteria, fungi, and polymorphonuclear leukocytes as these may interfere with scoring. Slides are then scored at 100x (oil immersion lens). Smeared, clumped overlapped or necrotic cells or those without intact nuclei are not recorded. Only those micronuclei are noted which are a) rounded or oval shaped; b) less than one-third the diameter of the main nucleus; c) in the same focal plane as the nucleus; d) of the same color, texture, and refraction as the main nucleus; and e) clearly separated from the main nucleus.

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Chapter

〖Social and Psychological Impact〗

Arsenicosis can produce a variety of non-clinical social effects, some of which have been documented in countries like Bangladesh and West Bengal (India). Melanosis does not create any problem at all. It is the keratosis, particularly palmar keratosis creates problem. For example, children with palmar arsenical keratosis are not being sent to school to hide the evidence of arsenicosis. Similarly, young women with palmar arsenical keratosis unable them to get married, force to divorce or adopting the borkha. It has profound impact on individual and community level with wrong information to some people about its contagious nature that isolates the patient from school and social involvement.

In addition, some people in those areas believe that: a) such a girl would cause unhappy family conditions, b) such a girl would be sexually

malfunctioned, c) arsenic causes considerable physical damage to a girl and d) additional money will be required for treatment of a newly married woman.

In the poor family domestic water collection and its management is predominantly undertaken by women and girls, who spend considerable amount of time and energy under various conditions on each day to collect drinking water for their families (Crow & Sultana 2002). It is rare for men to participate in domestic water collection.

Arsenic-related weakness and illness causes further economic damage, as people suffering from arsenicosis were increasingly unable to work (Ahmed, 2002). Most of the cases of arsenicosis cannot afford their treatment cost which leads to social crisis and distress selling (Sarker, 2008).

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✶ Myth 1

Arsenicosis is an evil spirit/God's curse/sin/contagious disease?

Chapter

6

〖Method of Arsenic Estimation〗

The amount of arsenic in water, soil, air, foodstuffs, and biological samples (blood, urine, nail, hair) can be estimated by a number of methods, ranging from the simplest Gutzeit's test to ICP-MS. Several points are considered before selection of any of the following methods: a) qualitative or quantitative test, b) field-based or laboratory based, c) immediately done or time consuming, d) cheap or costly, e) require less skill or experienced, and f) estimation of total arsenic or speciation.

Qualitative method: Marsh test or Gutzeit's test can be used for initial screening purpose at the field level. In addition, this method is preferred where a large number of samples need to be estimated such as in Bangladesh, India or China.

Semi-quantitative method: This method is more reliable than the qualitative

method. Like qualitative method, this method can be used for the estimation of total arsenic in the water samples of all hand pump tube wells of the country like Bangladesh, India or China, where it is a gigantic task that involves technical, institutional, and social challenges. Initial screening and regular monitoring of all the tube wells water are almost impossible using atomic absorption spectrophotometer. In this situation, kit method can be used at the field level.

Quantitative method: This method is the most preferred method. The instruments used for the estimation of total arsenic level are UV-Vis spectrophotometer, atomic absorption spectrophotometer with either hydride generator or graphite furnace, and atomic fluorescent spectrometry (AFS). Speciation of arsenic (As^{III}, As^{V}, MMA^{III}, MMA^{V}, DMA^{III}, DMA^{V}, arsenicholine, arsenibutaine, arsenosugars, etc) is estimated by high performance liquid chromatography-atomic fluorescence spectrometer (HPLC-AFS), inductively coupled plasma-mass spectroscopy (ICP-MS) and HPLC-MS/MS. When two or more instruments are joined they are called hyphenated method. These hyphenated methods are expensive.

Table 6.1 *Detection limit of arsenic in water using deferent methods.*

Method	Detection limit (ppb)
ICP-MS	1
Atomic absorption spectrophotometer with hydride generator	2
Atomic absorption spectrophotometer with graphite furnace	5
UV-VIS spectrophotometer	8
Kit method	50

(Misbahuddin and Khandker, 2011)

The limit of detection of each quantitative method is important (Table 6.1). The spectrophotometric method of total arsenic estimation is the silver diethyldithiocarbamate (SDDC) method which is more sensitive than the kit

method. The limit of detection using ICP-MS is 1 ppb whereas it is 50 ppb in kit method.

6.1 Marsh Test

The test was named from its inventor, the English chemist James Marsh (1794-1846) and was first published in 1836.

Principle: Arsenic produces arseneuratted hydrogen in presence of zinc and sulfuric acid. This arsenic is deposited on the glass.

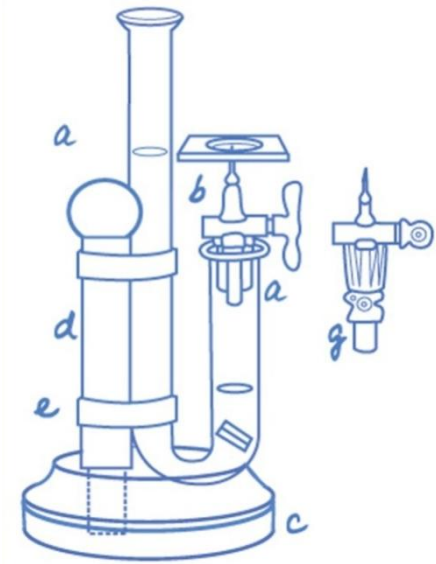

Figure 6.1 *Schematic diagram of the apparatus used in Marsh test. a) A glass tube open at both ends and about three quarters of an inch in its internal diameter. It is bent into the form of a siphon, the longer leg is about 8 inches in length and the shorter leg is about 5 inches; b) stopcock ending in a jet of fine bore; c) wooden block for the reception of the lower part of the pillar (d) with two elastic slips (e); f) horizontally piece of window-glass over the stopcock placed in such a manner as to retard slightly the combustion, the arsenic (if present) will be deposited on the glass; g) a small glass bucket.*

Procedure: A glass rod (1 inch) is to be dropped into the shorter leg followed

by a piece of zinc (1.5 x 0.5 inch) (Figure 6.1). The fluid to be examined for arsenic is mixed with 5 mL dilute sulfuric acid (acid: water 1:7) and poured into the long leg. Bubble gas appears from the zinc which is pure hydrogen, if no arsenic is present. But if the sample contains arsenic, the gas is arsenuretted hydrogen. The first portions are allowed to escape (air) by opening the stopcock and then closed. A portion of gas gives pressure of a column of fluid 7-8 inches high when the stopcock is opened. The gas is propelled with some forces through the jet. On igniting it, arsenic is deposited in the metallic state on the glass (Marsh, 1836).

Advantage: Marsh test does not require any instrument to estimate the presence of arsenic. It can be done by a less skill person within a short time. This method is suitable for field level detection of arsenic.

Disadvantage: Marsh test is a qualitative method. Now-a-days this method is rarely used. There may be false positive result due to presence of antimony.

6.2 Gutzeit's Test

Gutzeit's test is named from a German chemist, Max Adolf Gutzeit (1847-1915).

Principle: Arsine is formed from arsenic compounds by the addition of zinc granules to concentrated sulfuric acid (Nadeau, 1952). The arsine is detected on a strip of filter paper as gray spot (moistened with silver nitrate) or yellow to reddish-brown spot (moistened with mercuric chloride).

Procedure: A wide-necked bottle (200 mL) or conical flask is closed by a rubber bung perforated with one hole, in which it is held vertically a narrow glass tube (3.5 x 1 inch) (Figure 6.2). The tube is loosely packed with a wad of

glass wool impregnated with lead acetate to remove hydrogen sulfide from the evolved gases. It is closed at the upper end by a rubber stopper perforated by a hole (5 mm diameter). The top surface of this stopper is flat on which a mercuric chloride paper is laid during estimation. The paper is kept in place by a loose cape made of a disc of glass (5 cm).

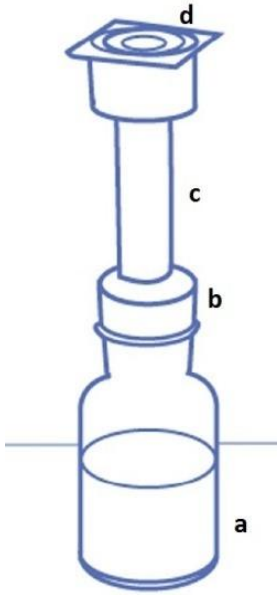

Figure 6.2 *Schematic diagram of the apparatus used in Gutzeit's test. a) A glass bottle containing arsenic, zinc and sulfuric acid; b) rubber with bore; c) narrow glass tube containing glass wool impregnated with lead acetate; d) a filter paper at the top of the glass tube containing either silver nitrate or mercuric chloride.*

Advantages: Gutzeit's test does not require any instrument to detect the presence of arsenic in the sample. Simply, a bottle or conical flask, filter paper, glass wool, silver nitrate, and mercuric chloride are required. It can be done by a less skill person within a short time. This method is suitable for field level.

Disadvantages: Gutzeit's test is a qualitative method. Silver nitrate is light sensitive. The sensitivity of this method is about 1 μg. It is only applied for the

estimation of arsenic in water or urine.

6.3 Field Test Kits

Several commercial field test kits (E. Merck kit, HACH kit, Arsenator 36, Wagtach Digital Arsenator, CMC kit, NIPSOM kit, ITN-BUET kit and GPL kit, etc) are available for the determination of total arsenic in tube wells water (Figure 6.3; Table 6.2). The field test kit must be simple, cheap, accurate, precise, safe, rapid and reliable. The existing kits do not fulfil all the criteria.

Figure 6.3 *Different kit methods for rapid estimation of arsenic.*

Principle: As^{V} is converted to the As^{III} form in water by the addition of potassium iodide and stannous chloride. Addition of zinc and hydrochloric acid to the water sample liberates nascent hydrogen that reacts with the As^{III} to

release arsine gas. The arsenic reacts with mercuric bromide paper to form complex salts of arsenic and mercury, producing yellow to brown stain depending on the arsenic concentration in the sample. This coloration is due to the formation of the compounds $H(HgBr)_2As$ (yellow), $(HgBr)_3As$ (brown) and Hg_3As_2 (black). At low concentration of arsenic a yellow stainning is produced while high level gives a black stainning (Pande et al., 2001).

In case of Merck kit test strip: If the strip turns yellow, then it means arsenic concentration is 100 pp or more; turns pale yellow means arsenic concentration is in between 1-100 ppb; if remains white it means there is no arsenic. That is, the range of arsenic is very wide.

Advantages: Field test kit is simple, low-cost method for initial screening of arsenic in hand pump tube well in shortest possible time.

Table 6.2 *Field kits used in Bangladesh.*

Name	Country of origin
E. Merck field kit	Germany
HACH kit	USA
NIPSOM kit	Bangladesh
ITN-BUET kit	Bangladesh
GPL kit	Bangladesh
AIIH&PH kit	India
CMC kit	China
AAN-Hironaka kit	Japan
Aqua kit	India
Arsenator 36	Austria
Wagtech Digital Arsenator	UK
PeCo 75	Austria

Disadvantages: Field kit provides a semi-quantitative result and the re-liability of this type of field kit is questionable because of poor accuracy (Rahman et al., 2002). Ten to seventeen per cent of the samples show false negative.

Reproducibility of result by the kits at the lower level of arsenic is found unsatisfactory. Field test kit produces arsine gas which is toxic. Mercuric bromide paper used is also toxic. Silver nitrate is light sensitive. This method provides qualitative and semi-quantitative method of total arsenic estimation. Kit method is not able to detect arsenic level of 10 ppb. There is inacuracy of data when the concentration of arsenic is 100 ppb or more.

6.4 Spectrophotometric Method

This is the most widely acceptable method for the estimation of total or speciation of arsenic in water, hair, nail and urine. This method was reported in 1959 (Powers et al., 1959).

Principle: This method consists of digestion of sample and generation of arsenic. In the process of digestion, the sample containing arsenic is to be digested with four acids: sulfuric acid, nitric acid, hydrochloric acid and perchloric acid. Digestion is considered to be completed when there apprears white fume. After digestion, the inorganic arsenic in a sample is reduced by acid zinc reaction to arsine (AsH_3) which is scrubbed through lead acetate impregnated glass wool and is absorbed in SDDC dissolved in pyridine. This step is done with the help of arsenic generator (Figure 6.4). The color developed due to arsine-SDDC and the reading is taken at 535 nm (Figure 6.5) by spectrophotometer. 1-Ephedrine in chloroform has been found to be a suitable solvent for SDDC if the analyst finds the odor of pyridine objectionable. In case of speciation, the sample must be passed through a column in order to separate MMA, DMA, and inorganic arsenic. Then these are estimated by spectro-photometer using the procedure same as total arsenic.

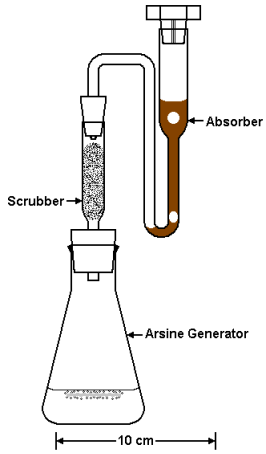

Figure 6.4 *Schematic diagram of arsine generator.*

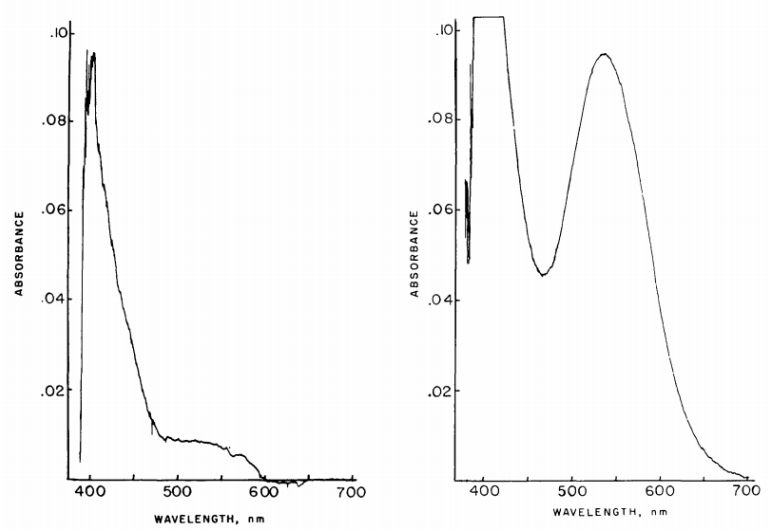

Figure 6.5 *Absorbance spectrum of reagent blank (left) and arsenic (2 µg; right) recorded against a SDDC method using spectrophotometer.*

Advantage: The limit of detection of total arsenic in water using SDDC is 10 ppb.

Disadvantages: Several metal ions-chromium, copper, mercury, molybdenum and antimony may interfere in the determination of arsenic in water. It is more expensive than Gutzeit's method but cheaper than HG-AAS or HPLC-HG-AFS.

6.5 Atomic Absorption Spectrometer

Arsenic can be estimated by atomic absorption spectrometer (flame, with hydride generator or graphite furnase). Usually atomic absorption spectrometer (flame) is not recommended for arsenic estimation. Atomic absorption spectrometer (graphite furnase) is better than atomic absorption spectrometer (flame). Atomic absorption spectrometer (with hydride generator) is the most sensitive method among these.

Principle: This procedure is used for the quantitative determination of arsenic employing the absorption of optical radiation (light) by free atoms in the gaseous state (Figure 6.6). A sample in the atomizer is measured using a detector, and the ratio between the two values (the absorbance) is converted to analyte concentration or mass using the Beer-Lambert Law.

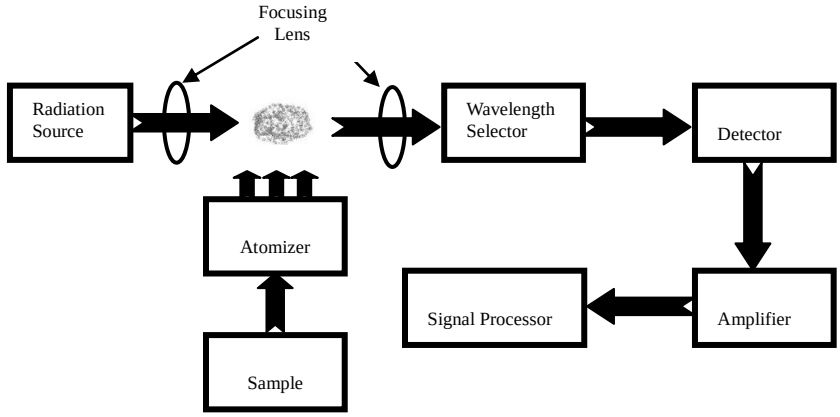

Figure 6.6 *Schematic diagram of atomic absorption spectrometer.*

Advantages: It is more sensitive than SDDC method.

Disadvantages: It is less sensitive than atomic absorption spectrometer hydride generator. Flame atomizer is not recommended for estimation of arsenic. However, graphite furnace spectrophotometer may be used.

6.6 Hydride Generation Atomic Absorption Spectrometer (HG-AAS)

Principle: HG-AASinduces the reaction of sodium borohydride with reduced arsenic species (As^{3+}) to produce volatile hydrides which are purged from solution and detected by spectrometry.

Advantages: The limit of detection is 0.02 ppb. It is more sensitive than atomic absorption spectrometer (flame).

Disadvantages: Speciation of arsenic cannot be estimated by this method. In addition, the complexity of the sample matrix can alter the efficiency of the reduction procedure or the hydride generation reaction. The interferences from transition metals, dissolved organic carbon, and salinity are very well documented and allow for significant biases associated with complex matrices, especially at trace levels.

6.7 Voltammetric Stripping Technique

Voltammetric stripping technique is useful for on-site analysis, providing accurate measurements of low concentrations with rapid analysis times and low cost/weight instruments (Feeney & Kounaves, 2002). It provides an effective and reliable method to analyze arsenic at the ppb levels found in drinking water. The method involves cathodic or anodic stripping voltammetry using a pulsed

wave form.

6.8 HPLC-HG-AFS

HPLC-HG-AFS method uses ion-exchange liquid chromatography coupled on-line to atomic fluorescence spectrometry through continuous hydride generation. HPLC is used for chromatographic separation of speciation of arsenic compounds (As^{III}, As^{V}, MMA, DMA) (Figure 6.7).

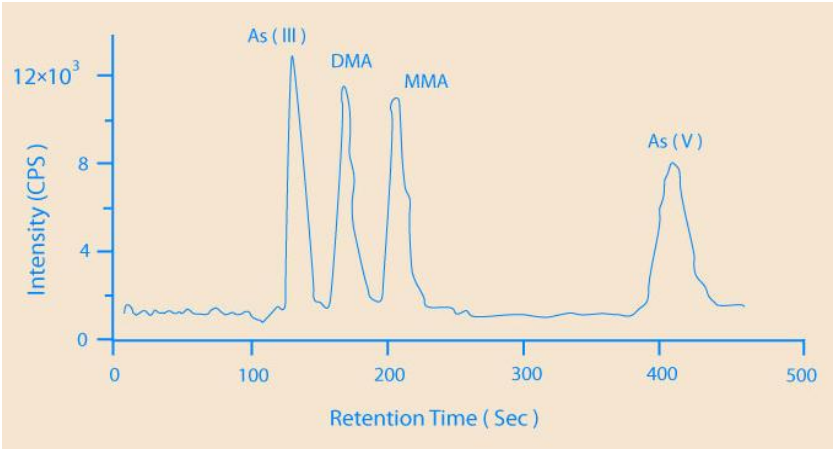

Figure 6.7 *Speciation of arsenic using HPLC-HG-AFS (Le, 2001).*

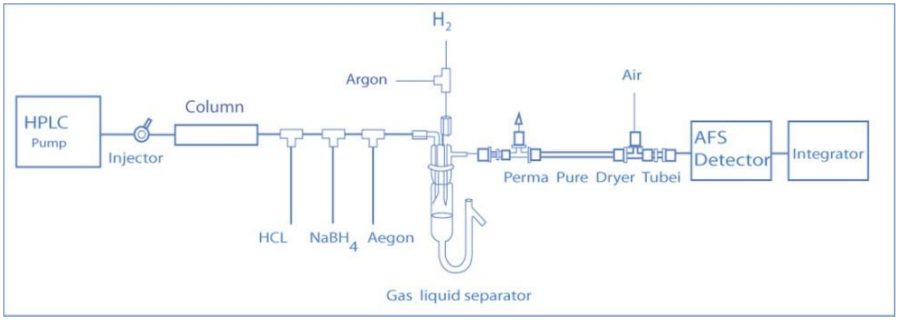

Figure 6.8 *Diagrammatic scheme of HPLC-HG-AFS (PS Analytical application note 024).*

Procedure: Sample containing arsenic is injected into the HPLC system containing strong anion exchange columns and a gradient is performed by changing from 10 mM to 60 mM phosphate buffer solution (Figure 6.8). Hydrochloric acid and $NaHB_4$ are added by peristaltic pump for reaction with arsenic for hydride generation. The flow rate of the mobile phase is 1 mL/min. The volatile arsine is produced which is carried by argon gas to the gas liquid separator and finally to the atomic fluorescence detector.

Advantages: The limit of detection is as low as 0.1 ng for arsenic and its metabolites. All compounds are detected within 10 min after injection of the sample into the HPLC pump.

6.9 ICP-MS

The inductively coupled plasma mass spectrometry (ICP-MS) is a technique that combines a high-temperature (95,000-10,000 K at atmospheric pressure) inductively coupled plasma source with a mass spectrometer. It allows the analyst to identify and quantify the multiple elements including arsenic at high speed. The technique was commercially introduced in 1983. An aerosol of the sample is introduced into the plasma source where vaporization, atomization and ionization of the analyte occur nearly simultaneously. Elemental ions are passed into a mass spectrometer.

Procedure: The instrument should be started according to the standard operating procedure. After ~30 min warm-up, tune ICP-MS normally. The performance should be check with default specifications. The peristaltic pump is used to introduce arsenic at a concentration of 10 ng/g in mobile phase directly into the nebulizer (Figure 6.9). One has to ensure that the signal for m/z 75 response is within normal range. The nebulizer tube is connected to a 3-way

tee. Internal standard should be delivered via peristaltic pump with a flow rate of approximately 0.04 mL/min into one port of the tee. The flow from the HPLC column should be connected to the third port of the tee. All connections should use PEEK fittings. ICP-MS is connected with HPLC. The flow (1 mL/min) of HPLC is started. Ensure proper flow and adequate drainage of ICP spray chamber (>1 mL/min). At the sametime check for leaks. Allow time for column and plasma to equilibrate. Set ICP-MS acquisition method for time-resolved collection of m/z 72 and 75 with integration (dwell) times of 0.2 and 0.8 s, respectively, and 1 replicate (read) per point. Analyze a blank (mobile phase only) solution to verify that mobile phase and chromatography vials are arsenic-free. Monitor instrument conditions to ensure operation is stable and within normal functioning range.

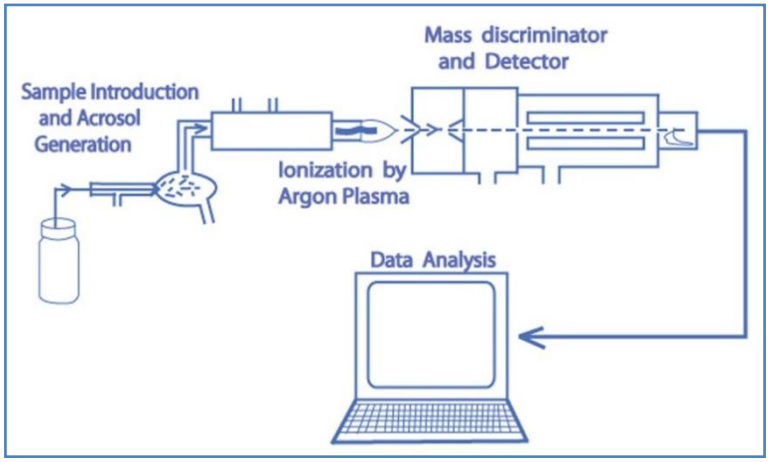

Figure 6.9 *Schematic diagram of ICP-MS.*

Advantages: ICP-MS offers advantages over general speciation analysis including: multi-element and multi-isotope detection (Figure 6.10). The estimation can be done quickly. Detection limit for arsenic is better than that obtained by graphite furnace atomic absorption spectroscopy.

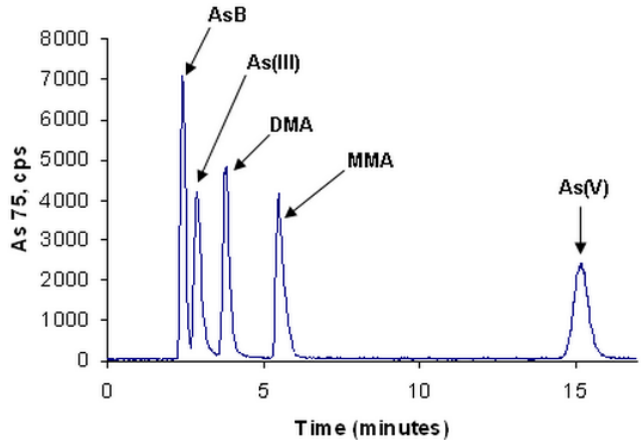

Figure 6.10 *Typical HPLC-ICP-MS chromatogram of an arsenic multianalyte working standard solution (5 ng/g).*

Limitations: This method is costly. Arsenic estimation may have a spectral interference under certain conditions. Argon from plasma gas and chlorine from the sample matrix may combine to form $^{40}Ar^{35}Cl$ which has the same nominal mass-to-charge ratio as arsenic. The monitoring signal at m/z 75 comes from two sources (the arsenic and the argon chloride interference) (B'Hymer & Caruso, 2004). It generally requires a clean room environment for ultra-low detection limit.

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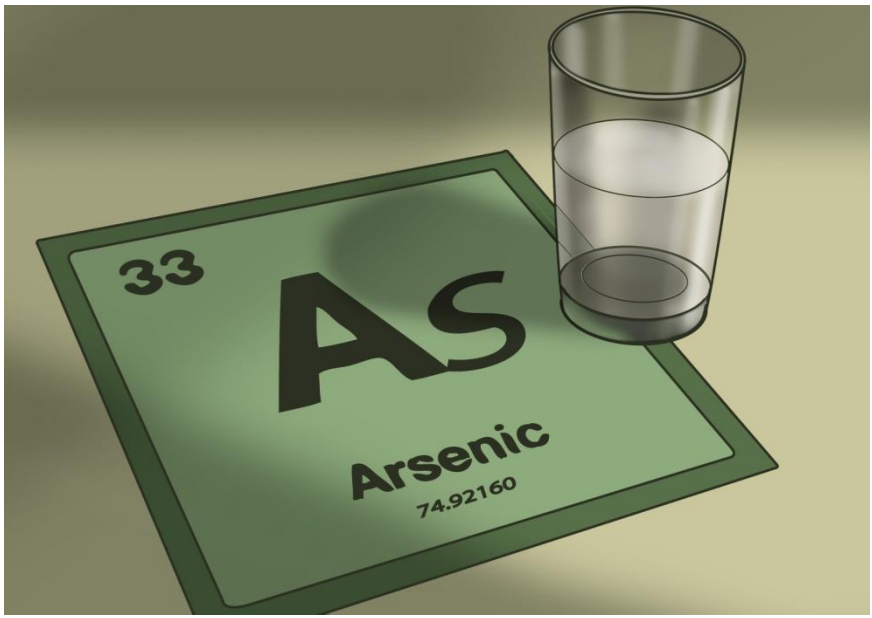
✶ Myth

Presence of arsenic in drinking water can be detected by immersing guava leaf.



Use surface water, stop digging

Chapter

7

〖Providing Arsenic Safe Drinking Water〗

"Arsenic mitigation solutions showed significant microbial contamination and none can provide 'safe' drinking-water."

M. Feroze Ahmed, Bangladesh University of Engineeringand Technology

The first choice of treating non-malignant skin manifestations of arsenicosis is to provide arsenic safe drinking water if it is due to drinking arsenic contaminated water. Arsenicosis due to inhalation of arsenic polluted air is not effective using this measure.

Four questions must be considered before thinking to provide arsenic safe drinking water (Ravencroft et al., 2009): a) who will be the user? (household, rural community or municipality); b) who will implement it? (household,

commercial level, non-government organization or government); c) who will finance?; d) is the water be able to free from any chemical or microbial?

We have to find out the simplest, cheapest, and quickest solution of providing arsenic safe drinking water.

The first step is the screening of arsenic contaminated tube wells. Even in arsenic endemic area, all the hand pump tube wells are not equally contaminated with arsenic. After identification, hand pump tube wells are colored with red (>50 ppb) or green (<50 ppb) marking ("traffic light" colors; Figure 7.1). However, red marked (high arsenic containing) tube well water may be used safely for washing laundry. The simplest and most immediately achievable option is the sharing of green marked hand pump tubewells or red marked tube wells that contain relatively low concentration of arsenic. The latter option is particularly applicable where 70-100% hand pump tube wells are contaminated with high concentration of arsenic. The number of people per green-marked tube wells has increased many times without facing any practical difficulties to share (van Geen et al., 2002). The red or green color coding should be monitored time to time, as tube well with previously safe test result may be later found to contain increased level of arsenic.

The available options for arsenic safe drinking water are: surface water, groundwater and rainwater. We give emphasis on two terminologies applicable to provide arsenic safe drinking water: mitigation and remediation. Mitigation means the provision of alternative arsenic-free water whereas remediation means arsenic removal from extracted water (Garelick et al., 2005).

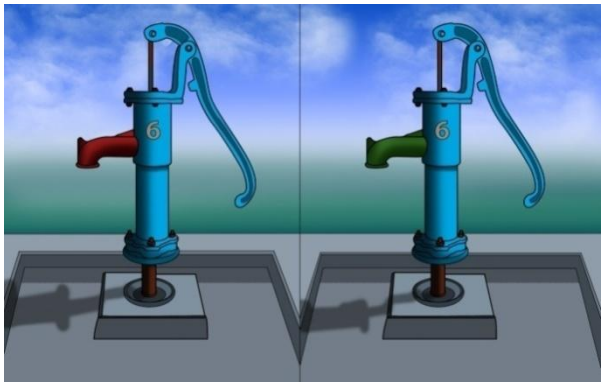


Figure 7.1 *Red (left) and green (right) marking of hand pump tube wells.*

Mitigation

Mitigation includes pond sand filter, rain water harvesting, dug well, and supply of tap water collected by deep tube well. Detail discussion on this topic has been done in a book (Ahmed and Ahmed, 2002).

7.1 Pond Sand Filter

Principle: Pond sand filter consists of a tank containing the bed of filter materials and a storage chamber. Water is pumped into the pond sand filter tank using a hand pump tube well head connected to a pipe which intakes water from the pond (Figure 7.2). It then flows vertically through the sand bed. At the bottom of the tank an under drain system (the 'filter bottom') is placed to support the filter bed. The bed is composed of fine sand, usually free from clay, loam and other organic matters. The filter bed normally is 1.0-1.5 m thick, and the water to be treated stands to a depth of 0.3-0.5 m above the filter bed. From the base of the filter bed the water is discharged into a storage chamber.

Advantage: This system is preferable where there is an abundance of surface

water, for example, in Bangladesh. There is no need of chemical treatment. One pond sand filter can supply the daily requirement of drinking and cooking water for about 40-60 families.

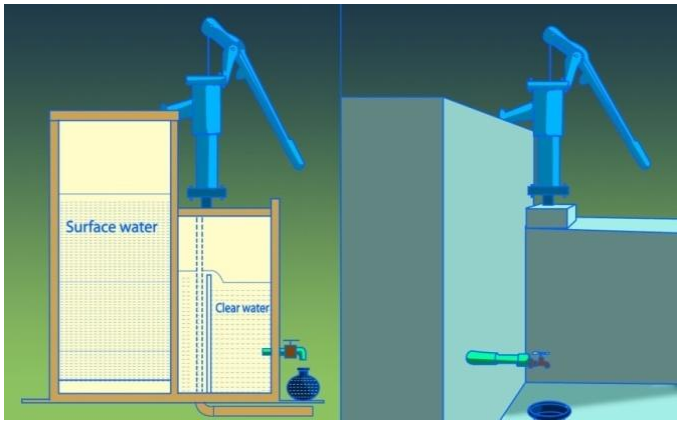


Figure 7.2 *Schematic diagram of pond sand filter.*

Disadvantage: This method is not applicable where there is no pond. The use of pond sand filter may be sometimes interuppted for maintenance. The suspended matter present in the raw water is largely retained in the upper 0.5-2.0 cm of the filter bed. This allows the filter to be cleaned by scraping away the top layer of sand. The filter cleaning operation takes one day. But after cleaning, one or two more days are required for the filter bed to again become fully effective. Trained caretaker is needed for maintaining the pond sand filter. Pond which is used for fish culture, agricultural and domestic runoff, latrine discharges, and washing livestock is not suitable. So, it is sometimes difficult to get such pond in arsenic endemic area. Owner of the pond will not restrict its use only for the supply of drinking water considering commercial point of view.

Some of the pond sand filters are abundant after implementation (BRAC, 2000). This type of pond sand filter is not feasible.

7.2 Rain Water Harvester

Rainwater harvesting technique is practiced in many parts of the world for more than 4,000 years. There is a long-established tradition of rainwater collection in some parts of Bangladesh, where groundwater is heavily contaminated with arsenic, iron, and salinity.

The success of rainfall harvesting depends upon the frequency and amount of rainfall. It is not a dependable water source during dry season or prolonged drought. The total annual rainfall in India is 400 million hectare meters (area x height) whereas the total area of India is 329 million hectares. This gives us an example, how much rainwater we can use properly with good planning. The desert receives less than 200 mm of raining annually whereas Cherrapunji (India) receives 11,400 mm annually. The use of umbrella can protect you from raining. In addition, it can be used to collect rain water for drinking purpose in order to avoid the use of arsenic contaminated drinking water (Figure 7.3). This motivates you but the process is difficult to implement.

Figure 7.3 *Dual use of umbrella.*

Principle: A rain water harvester is constructed using pre-cast concrete blocks. Water is channeled from collection pipes on the roof into the rain water

harvester through a funnel with a mesh filter (Figure 7.4). The rain water harvester is covered with a lid. The first collected rainwater may carry significant amounts of contaminant (debris, dirt, dust) which accumulate on the roof and in the gutters. It is, therefore, recommended not to collect the first flush of rainwater. A cover for the intake is provided and users are instructed to remove these 5/10 minutes after the rainfall started.

Advantage: Initial investment and maintenance are not costly. A large number of families can be benifited if properly maintained in an area where the amount of rainfall is large like India or Bangladesh. Good quality water can be stored if collected properly. It is an effective method of supplying drinking water in coastal areas where salanity is a problem. This method of water collection is suitable for tin-roof houses. Alternative arrangement can be made by using polythene or thick clothes on the roof of house to collect water.

Figure 7.4 *Rain water harvesting.*

Disadvantage: Its success also depends on communities that consider water

supply a priority. The quality of the collected water can be improved by proper maintenance of the roof and gutters and careful cleaning at the beginning of each wet season. There is shortage of water during the dry season. As the water is mineral-free, some people may dislike it due to its tasteless.

7.3 Dug Well

Dug well is the oldest method of collection of potable water from the ground. The use of dug wells in Bangladesh has declined since the 1960s following the introduction of the hand pump tube wells.

Principle: Dug well may be converted into hand pump sanitary dug well. The well is covered and water is drawn from the well using a hand pump (Figure 7.5). An apron is constructed around the well to prevent contamina-tion from the surface. Following digging/excavation the well is lined with local materials, either concrete or clay rings to prevent the walls from collapsing. Proper lining and a well-designed apron are crucial for prevention of surface water contamination.

Advantage: In Bangladesh, the water of dug well water contains safe concentration of arsenic. The wells are cheaper and easier to construct. Usually no special equipment or skill is required for the construction of dug well.

Disadvantage: Percolation of contaminated surface water is the most common route of pollution of well water. It is, sometimes, difficult to protect the water from bacterial contamination.

It may be possible to combine dug well with home-based surface water filter to provide a socially acceptable, bacteriologically safe water source for rural household.

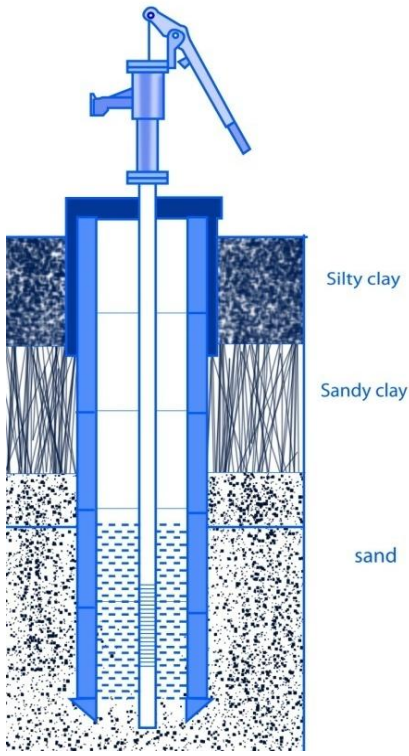


Figure 7.5 *Schematic diagram of dug well with sanitary protection.*

7.4 Community Water Supply

Principle: Like urban area, surface water with treatment or groundwater with safe level of arsenic are directly pumped into a water tank and then supplied to the houses by pipe line (Figure 7.6).

Advantage: This has contributed significantly to both the reduction and control of water-related diseases. It reduces the burden of water collection, which is borne especially by women and children.

Disadvantage: The total cost of a piped water scheme depends on the type

that is, household or stand post type connection, size and distribution of the settlements, etc. The construction cost may vary from US$ 25,000 and above. It needs regular operation and maintenance cost.

Figure 7.6 *Community water supply.*

7.4.1 Remediation

Several physico-chemical techniques are recommened for the removal of arsenic from arsenic contaminated drinking water, both on-site and off-site, especially in the area where most of the tube wells are contaminated. The most commonly used technologies are oxidation, co-precipitation followed by adsorption onto coagulated flocks, lime treatment, ion exchange, adsorption onto various solid media and membrane filtration. They may be used alone or in combination. Remediation also includes household filters, phytoremediation and solar-light assisted arsenic removal**.**

7.5 Oxidation

Principle: Oxidation is a required step to transform As^{III} species in more

easily removable As^{V} species by chemicals like gaseous chlorine, hypochlorite, ozone, permanganate, hydrogen peroxide, manganese oxides and Fenton's reagent (H_2O_2/Fe^{2+}). This reaction process is very fast for permanganate, chlorine and ozone in comparison to hydrogen peroxide and chloroamine.

Advantages: Among them gaseous chlorine is a rapid and effective oxidant, but it reacts with organic matter, producing toxic and carcinogenic trihalomethanes. Potassium permanganate effectively oxidizes As^{III}, and it is inexpensive and suitable for developing countries. Hydrogen peroxide is an effective oxidant if the untreated water contains dissolved iron, which occurs in conjunction with arsenic contamination, allowing the occurrence of Fenton reactions. It is a simple process with low operation cost. It can be applicable for large volume of arsenic contaminated water.

Disadvantages: An adequate selection of oxidants in relation with aquatic chemistry and water composition is a pertinent step to achieve a high removal efficiency of aqueous arsenic by oxidation. Toxic chemicals and carcinogens are produced as by-products. Interfering substances may decrease the arsenic removal efficacy. Due to several drawbacks, oxidation alone is not an effective method for removal of arsenic. Another method must be included (precipitation of As^{V}). As^{V} adsorbs more easily onto the solid surfaces than As^{III}.

7.6 Coagulation and Filtration

Compared with aluminum coagulants, Fe^{III} salts have been found to be more effective for arsenic removal. Although the coagulation process is a simple and economically sound one, it produces a wet bulky sludge.

Principle: Chemicals such as aluminum sulfate, ferric chloride and ferrous sulfate, iron salts are used to remove arsenic (As^{V}), which adsorbs onto

coagulated flocs and then can be removed by filtration. As^{III} is at first oxidized with chlorine. Iron chloride generates relatively large flocs, while smaller ones are formed with ferrous sulfate. Filtration is a necessary step.

Advantages: It is a simple, most common, effective and low cost method acting over wide range of pH. Removal of As^{V} from water is high. Installation cost is small and it can be easily applied to large volume of water.

Disadvantages: Very high amount of coagulant is needed. Additional separation step is necessary. Without filtration, As^{V} removal is around 30%, but using a 0.1 or 1.0 mm filter, As^{V} removal improves to more than 96%. Further environmental pollution occurs due to improper disposal of contaminated sludge.

7.7 Adsorption

Because of the ease of handling, sludge-free operation, and possibility of regeneration, the adsorption process appears to be the most promising one. Activated alumina has long been the most often used adsorbent for arsenic removal. The problems including the need for pH adjustment, the relatively low adsorption capacity, and aluminum dissolution have prevented activated alumina from wider applications.

Cerium: An iron based inorganic adsorbent, developed by doping cerium ions into iron ions, is used for As^{V} removal. In terms of adsorption pH range and adsorption capacity, the new adsorbent demonstrated a much better performance than activated alumina (Zhang et al., 2003).

Advantages: It is comparatively cheaper and available commercially.

Disadvantages: It interferes from competitive anions (PO_4^{3-}, HCO_3^{-}, SiO_3^{2-}, SO_4^{2-}). Further environmental pollution occurs due to improper disposal of

contaminated sludge.

7.8 Ion-exchange

Advantages: The removal of arsenic is not depending on pH and concentration of the influent. It is moderately effective.

Disadvantages: The removal of As^{III} is not possible and prior oxidation is necessary. Other anions interfere the process. Iron may be clogg. It produces large volume of toxic brine during regeneration of resins.

7.9 Membrane

Advantages: The removal of As^{V} from water is good with no toxic waste product.

Disadvantages: Very low amount of As^{III} is removed. Pretreatment is often required. High initial and maintenance cost are required. It is not an effective method when water is highly contaminated with arsenic.

7.10 House-hold Filter

There are several house-hold filters: Safi filter, sono file, pitcher filter, etc (Figure 7.7). The three- or four-pitcher filter is based on an indigenous method of filtration, which has been used in Bangladesh for ages to remove excess iron and calcium from drinking water. The household level filtration device was designed to remove both arsenic and pathogenic bacteria.

Principle: The Safi filter consists of two concrete buckets (20 liter). One buchet is placed on the top of another bucket. The upper bucket is filled with

arsenic contaminated tube well water, which then flows through a permeable ‘candle’ and is collected in the lower bucket where it is stored. When needed it is drawn off with a tap. The Safi filter candle is prepared from a chemical mixture of laterite soil, ferric oxide, manganese di-oxide, aluminum hydroxide and meso-porous silica. These materials adsorb arsenic as the water passes through the candle and thus the contamination is removed.

Two local clay pitchers are used to filter water. The top pitcher is partially filled with sand and charcoal, and a small hole is made in the bottom. A piece of synthetic cloth is placed over the hole to prevent sand from spilling out. Water is passed through this pitcher to remove suspended matter from the surface water and arsenic as well as iron from tube well water. After passing through the top pitcher, filtered water is stored in the bottom pitcher. It is modified by adding a third pitcher above the sand/charcoal pitcher, which is filled with iron filings to provide an additional source of iron oxide to adsorb more arsenic.

Advantage: This filter can supply approximately 40 liters of water per day. The cost of such filter is approximately US$ 15. The candle eliminates pathogenic bacteria from the contaminated water. After two years of continuous use, the candle should be replaced with a fresh one. Each new candle costs around US$ 4. The total cost for developing pitcher filter is less than US$ 5. The three-pitcher system has enormous potential to provide an emergency drinking water source for the arsenic-affected rural area. It is based on an indigenous technology, cheap, and can be constructed with locally available materials.

The removal efficiency of arsenic by sono filter is high (up to 300 ppb). Each filter lasts for up to 5 years. Spent materials are non-toxic. This filter can supply approximately 80 liters of water per day which is sufficient for a family of 5.

Disadvantage: The filter has problem like flow rate and arsenic removal efficiency (BRAC, 2000). Sono filter is not as successful with extremely high concentration of arsenic. Regular cleaning is required to prevent bacteriological contamination.

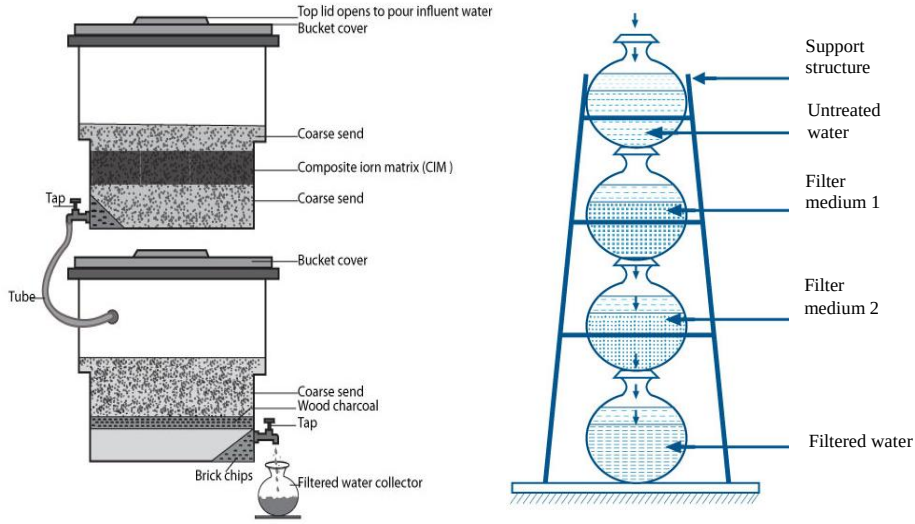


Figure 7.7 *Pitcher filter.*

7.11 Bishuddhya Filter

Principle: This is a plastic non-chemical based filter that does not remove arsenic, but instead is designed to remove bacteria from arsenic free surface water. The filtration and purification technique used in this system are similar to pond sand filter. The principal material used in this filter is different mesh sizes of locally available rocks. The water passes from the bottom through different layers to remove bacteria before it arrives at a storage chamber.

Advantage: Bishuddhya filter is relatively cheap. The cost for this household-based device is around US$ 45 with virtually no operation and

maintenance cost, except for washing the materials after a certain interval depending on the suspended loads of arsenic contaminated water.

Disadvantage: The only precautionary measure that needs to be ensured here is that surface water must be obtained from a protected source to ensure no contamination with chemicals, fertilizers, etc.

7.12 Activated Alumina Filter (ALCAN Filter)

Principle: The term 'activated' refers to the capacity of the alumina to enter into adsorption and/or catalytic reactions, and is determined largely by such variables as crystal structure, pore size and distribution, and the chemical nature of the surface. In this system there is adsorption of arsenic by activated alumina. The arsenic contaminated water passes through the activated alumina media and the treated water becomes arsenic free. Activated alumina is formed by the thermal dehydration (250-1150 ℃) of an aluminum hydroxide such as, gibbsite, bayerite, etc. Its principle characteristics are high surface area (>200 m^2/g) and associated porosity.

Advantage: Activated alumina is able to remove cations and anions by chemisorptions. This involves an ion exchange mechanism with the hydroxylated surface. It is able to remove a wide range of anions and cations such as arsenic, fluoride, chromium, zinc, iron, phosphates and organic materials. Arsenic removal efficiency is high. It is available to both community and household levels. There is no need to add any chemical. Each can provide 3,600 L of arsenic safe water per 12 hours for more than 100 families.

Disadvantage: The regeneration of saturated alumina is required once column is totally saturated. However, the efficiency of activated alumina decreases after regeneration. This method is pH sensitive and is high possibility

of media getting fouled or clogged by precipitated iron. The initial cost is high for both type of units: US$ 260 per unit (unit plus media), and US$ 52 (unit plus media) for the household based unit. Running cost is required because the activated alumina needs to be changed periodically. The replacement cost of media for community-based units is US$140 to treat 80,000 liters of water, and for household based unit it is US$ 12 to treat 11,000 liters of water. Apart from the cost which seems to discourage villagers, disposal of used material is also another issue of concern not only for this filter but also for all other arsenic removal filters.

7.13 Phytoremediation

Water hyacinth *(Eichhornia crassipes)* removes arsenic from arsenic-contaminated drinking water (Misbahuddin & Fariduddin, 2002). This effect depends on factors like the amount of water hyacinth, amount of arsenic present in the water, duration of exposure, and presence of sunlight and air. It provides a natural means of removing arsenic from drinking water at the household level without monetary cost. However, it is not clear where water hyacinth may influence bacterial contamination.

7.14 Solar-light Assisted Technology

Principle: Lemon juice (citrate) is added to a transparent bottle containing arsenic-contaminated waters, and left in the open air exposed to direct sun light for several hours (Figure 7.8). Iron should be added, if the required concentration is not naturally present. Due to the nature of the reaction, oxygen, iron, the irradiation source and an organic Fe^{III}-chelating compound are crucial to promote the reaction. After standing overnight, the Fe^{III} oxide precipitate is separated by

filtration (Hug et al., 2001). The optimum molar ratio for arsenic, citrate and iron is 1:4.5:18.7, respectively, over 90% of arsenic being eliminated after 4 hours of irradiation by visible light (black light, 360 nm) (Lara et al., 2006).

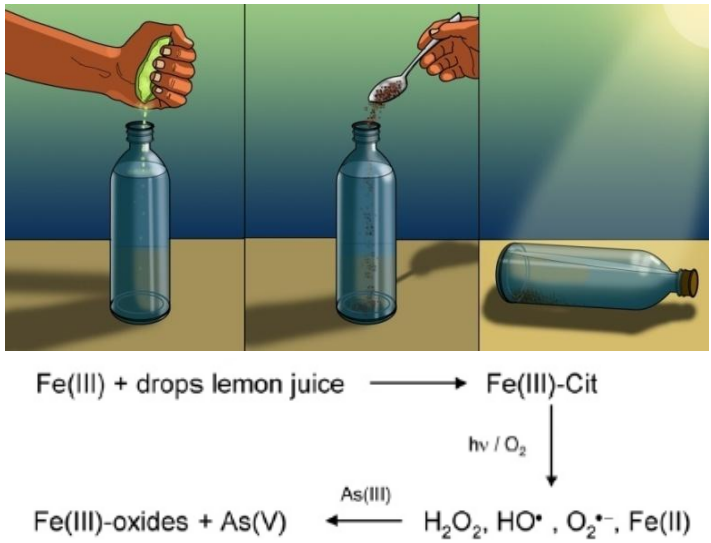


Figure 7.8 *Solar-light assisted arsenic removal (Litter et al., 2010).*

Advantage: The comparison between the As^{III} and As^{V} co-precipitation rates indicates that almost 80% of As^{III} is removed after 1 hour of irradiation, while As^{V} required 4 hours of irradiation to reach the same value. When natural water containing approximately 1 mg/L of arsenic, only as As^{V}, is irradiated with solar light under optimized conditions, approximately 95% of the arsenic is removed after 1 hours of irradiation.

Disadvantage: This procedure requires optimum concentration of arsenic, citrate and iron.

7.15 Overall Impression

All the options have advantages and disadvantages. Different methods are tried

in different countries (Table 7.1). Arsenic removal from waters is not an easy task. The selection of method depends on the economical aspect, size of the population, incidence of chronic illness, and lack of safe water. Sophisticated and expensive techniques cannot be applied in populations with low economic condition. In addition, these methods require continuous monitoring and maintenance cost. It needs awareness campaign by different stakeholders, villagers to understand the urgency of drinking arsenic safe water and re-sinking/reinstalling tube wells within 50-100 m depths. Periodic checkup of arsenic level in water is also vital.

Table 7.1 *Use of different options in Asian countries for removing arsenic from drinking water.*

Country	Dug well	Pond sand filter	Rainwater harvesting	Household water treatment	Community water treatment	Deep tube well
Bangladesh	√	√	√	√	√	√
Cambodia			√	√	√	
China					√	
India	√			√		√
Myanmar	√		√	√		√
Nepal	√			√	√	√
Pakistan	√			√		
Taiwan			√		√	
Vietnam			√	√	√	√

In some arsenic endemic areas of Bangladesh, more than 90% of hand pump tube wells are contaminated with high concentration of arsenic. In that case, the effectiveness of alternate water options are questionable. The affordability is also considered. Therefore, patient may consider the shifting of highly contaminated hand pump tube wells to low contaminated tube wells.

Proving arsenic safe drinking water is possible in Taiwan due to small number of people is affected whereas it is almost impossible in Bangladesh or India where millions of people are affected.

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✶ Myth 1

Use of green marked hand pump tube well water by the neighbor might decrease the amount of water. So, it should not be shared by other people who are using red marked hand pumped tube well water.

✶ Myth 2

Arsenic can be removed from water by boiling or filtering.

Agricultural land irrigated with high concentration of arsenic

Chapter

8

〖Removing Arsenic from Agricultural Land〗

The concentration of arsenic in soil varies that depends on: a) agricultural land (with or without irrigation, pesticide, fertilizer contaminated with arsenic), b) domestic garden, c) use of timber, d) mining area, and e) volcanic area. Irrigation of agricultural land with arsenic contaminated water shows high concentration of arsenic in soil. Country wise data of arsenic concentrations in soil are shown in Table 8.1. Average arsenic level in soil of Bangladesh is below 10 mg/kg, there is evidence that this value may exceed 80 mg/kg in places where arsenic-contaminated groundwater water is used for irrigation (Huq, 2008). In the past, numerous arsenical pesticides were used widely and, arsenic concentrations of 200-2,500 mg/kg occurred in the soil of orchards. Generally low amount of arsenic is present in the soil used for gardening. Sometimes the use of wood preservative containing arsenic may release arsenic from the wood of the house and contaminate the surrounding soil

by releasing arsenic. On the other hand, the soil near the volcanic area and mining is highly contaminated with arsenic. The levels of 100-2,500 mg/kg have been found in the vicinity of copper smelters.

Table 8.1 *Arsenic contents in the soil of various countries.*

Country	Amount of arsenic (mg/kg)	
	Mean	Range
Argentina	5	0.8-22
Bangladesh	22.1	9-28
China	11.2	0.01-626
India (West Bengal)		10-196
Japan	11	0.4-70
Italy	20	1.8-60
Mexico	14	2-40
United States	7.5	1-20

(Mandal and Suzuki, 2002)

The regulatory limit established by the UK is set at 10 mg/kg for domestic gardens and at 40 mg/kg for parks, playing fields, and open spaces (O'Neil, 1990). On the other hand, much tighter guidelines of 0.80 mg/kg for residential and 3.7 mg/kg for non-residential have been established in Florida, USA (Tonner-Navarro et al., 1988).

Speciation study shows that two most common arsenic in soil are the inorganic forms As^{V} and As^{III}. Organic arsenic includes MMA^{V} and DMA^{V}.

Therefore, it is important to remove arsenic from the soil of agricultural land. However, the arsenic level in plant is more correlated with the water arsenic than with the soil arsenic. There are several methods by which we can reduce the soil arsenic contents. These are: a) phytoremediation, b) use of cow-dung, and c) earthworm.

8.1 Phytoremediation

Phytoremediation (phyto = plant and remediation = correct evil) is an emerging technology that uses various plants to degrade, extract, or immobilize contaminants from soil and water. The term is relatively new, coined in 1991.

Advantages: Phytoremediation offers an environmentally-friendly and cost-effective method to remove arsenic from the contaminated soil. This type of plant is fast growing, has high biomass, be easy to harvest, and must tolerate and accumulate high concentration of arsenic.

Disadvantages: Plants are slow-growing with a small biomass and shallow root system. Plant biomass must be harvested and removed, followed by arsenic reclamation or proper disposal of the biomass. Arsenic may have a phytotoxic effect.

Pentavalent arsenic might be taken up by plants because it is similar to the plant nutrient phosphate. Poplars are grown in soil containing an average of 1250 mg/kg arsenic (Pierzynski et al., 1994).

A number of plants are suggested to be useful. These are *Pteris vittata (*Chinese brake fern) (Figure 8.1), *Pityrogramma calomelanos, Mimosa pudica*, *Melastoma malabrathricum, Nephrodium molle* (Figure 8.2) (Ma et al., 2001; Alkorta et al., 2004).

P. vittata can remove more than 95% of the soil arsenic (Doucleff & Terry, 2002) (Figure 8.3), whereas the removal by *Nephrodium molle*is about 68% (Hossain et al., 2006). *Pteris vittata* may hyperaccumulate arsenic to extremely high concentrations, up to 23,000 μg arsenic/g, in its shoots (fronds) (Ma et al., 2001).

Figure 8.1 *The fern Pteris vittata.*

Figure 8.2 *Pityrogramma calomelanos (A), Mimosa pudica (B), Melastoma malabrathricum (C), Nephrodium molle (D) can accumulate arsenic from the soil.*

This process does not result in the disappearance of the arsenic. During

phytoremediation, the arsenic moves from the soil to the fern fronds. It is then easy to harvest the fern fronds and further concentrate the arsenic in a safer location (Figure 8.4). Sometimes remediation processes result in complete destruction of the contaminant, as when microorganisms degrade polyaromatic hydrocarbons completely to carbon dioxide and water.

Colocasia antiquorum (arum), *Tagetes patula* (marigold) and *Ipomoea aquatic* (Kangkong) are also effective in removing arsenic from soil (Figure 8.5). Green and blue-green algae were found to hyperaccumulate arsenic from soil (Huq, 2008).

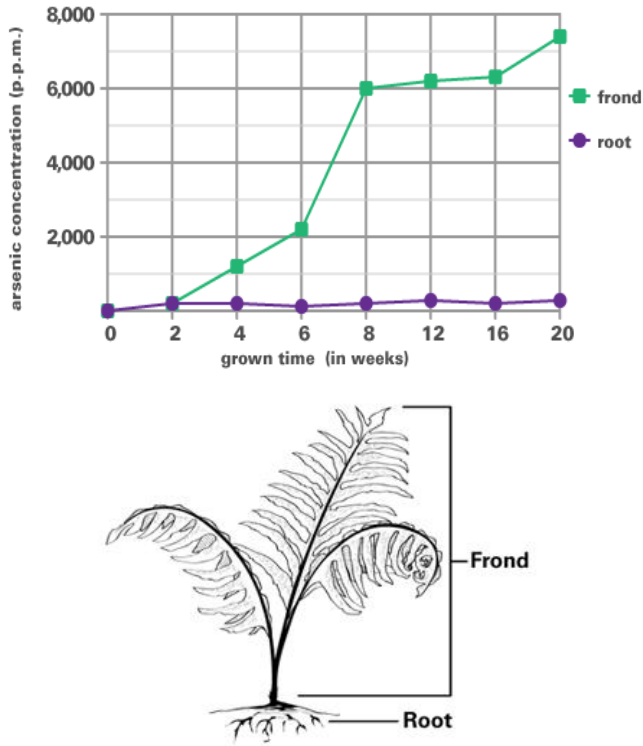

Figure 8.3 *Arsenic concentrations in fern Pteris vittata during growth in soil containing arsenic.*

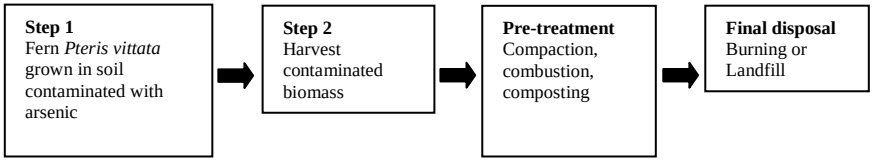

Figure 8.4 *Steps to disposal of arsenic in the fern Pteris vittata.*

Figure 8.5 *(A) Colocassia antiquorum (arum), (B) Ipomoea aquatic (Kangkong) and (C) Tagetes patula (Marigold) can be used to remove arsenic from arsenic contaminated soil.*

It is an excellent idea of cultivating ferns together with rice plants that could compete effectively in accumulating arsenic, thereby reducing the amount of arsenic reaching the rice plants (Tan et al., 2010).

8.2 Cow-dung

A method of arsenic remediation sludge should be mixed with cow-dung so as to form methylate arsenic which then no longer poses a risk (Rahman et al., 2013). The study was conducted in the laboratory under controlled condition and is yet to be tested in the field.

8.3 Earthworm

The common earthworm, *Eisenia fetida*, could also become a useful tool directly for remediation of arsenic present in landfill soil and demonstrated an efficiency of 42 to 72% in approximately two weeks for arsenic removal (Figure 8.6). Earthworm could offer an inexpensive and effective bioremediation alternative to complex and costly industrial cleanup methods. Arsenic resistant earthworm *Lumbricus rubellus* and *Dendrodrillus rubidus* can accumulate arsenic from soil up to 877 mg/kg earthworm (Button et al., 2009). *L. rubellus* is found to inhabit arsenic-rich soils that contains up to 34,000 mg arsenic/kg dry soil weight (Langdon et al., 2001). XAS analysis of *L. rubellus* suggests that 30% of As^{III} is coordinated with sulfurs, suggesting binding to metallothionein (Langdon et al., 2002). Metallothionein is a thiol-rich (approximately 30% of its amino acid sequence), low molecular weight (approximately 6000 Da), metal-binding protein that is present in abundant in the liver and kidneys of mammals. Its biosynthesis can be induced by steroids, hormones, cytotoxic agents, and a wide range of metals, including As^{III} (Garrett et al., 2001).

Figure 8.6 *Varieties of earthworm (A) Eisenia fetida, (B) Lumbricus rubellus and (C) Dendrodrillus rubidus that can be used to remove arsenic from arsenic contaminated soil.*

8.4 Questions to be Raised

1. Can we remove arsenic from the filter sludge by the earthworm?

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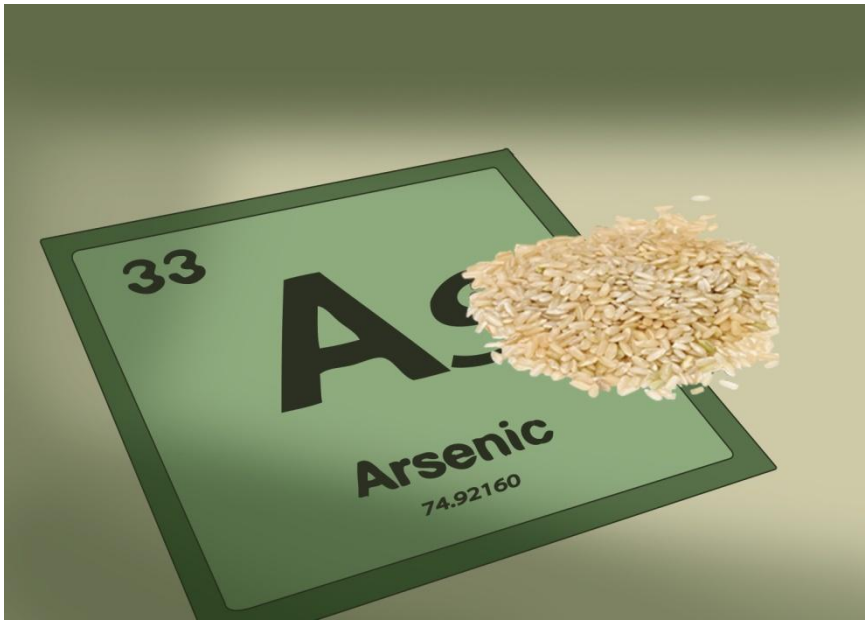

Screen foodstuffs for arsenic; Avoid or reduce the intake of food containing high concentration of arsenic

Chapter

9

〖Food with Low Arsenic Level〗

Food alone can contribute more than one-third of the total arsenic intake in arsenic endemic area (Huq, 2008) whereas drinking water contributes the rest two-third. This situation is observed in Bangladesh. Similar situation is thought to be in India. Therefore, necessary measure must be taken to reduce the intake of arsenic contaminated food or to take low arsenic contaminated food. However, unlike drinking water, the task to taking food low in arsenic is difficult to implement. In addition, the focus on the risk of consuming arsenic through drinking water and airborne workplace exposure are more highlighted than that of food. It may be due to failure of identification of health problem following chronic intake of arsenic contaminated food.

Seafood is an important source of arsenic intake. For example, it is about 90% of daily arsenic intake in the United States (Gunderson, 1995), 70% in Canada

(Dabeka et al., 1993), and 60% in Japan (Tsuda et al., 1995). In addition, Japanese consume seaweed which also contains arsenic. The amount of inorganic arsenic in seafood is very low. Most of them are in organic form. There is no reported case of poisoning following intake of high arsenic contaminated seafood. It is considered that ingestion of complex organic arsenic is safer than inorganic arsenic. In addition, the lethal dose of arsenic varies in rat (Table 9.1).

Table 9.1 *Median lethal dose of some arsenic species in rat.*

Species	Dose (mg/kg)
Arsine	3
As^{III}	14
As^{V}	20
MMA	700-1,800
DMA	700-2,600
Arsenocholine	6,500
Arsenobetaine	>10,000

The important sources of inorganic arsenic containing foods are rice, grains and flours (Schoof et al., 1999). In addition, rice has the tendency to bind with inorganic arsenic while washed or cooked with arsenic contaminated water.

In arsenic endemic areas, the use of arsenic contaminated water for irrigation has lead to the accumulation of arsenic in surface soil lead to bioaccumulation of arsenic in edible plants and crops (Bundschuh et al., 2012).

Arsenic is present in most of the foodstuffs. The estimated average daily dietary intake of arsenic in different countries is not known. However, it is estimated to 25-75 g/day by US adults.

9.1 Rice

Rice is the staple food for over half of the world's population. Over 90

percent of the world's rice is produced and consumed in the Asian region by 6 countries (China, India, Indonesia, Bangladesh, Vietnam and Japan) comprising 80% of the world's production and consumption. The people in Bangladesh and India (West Bengal) consume on average 450 g (range 400 to 650 g) of uncooked rice per person per day (Duxbury et al., 2003). Daily rice consumption per person by Japanese or Korean is 165 g or 185 g. Indian and Chinese consume low amount of rice in comparison to the people of Myanmar, Vietnam and Bangladesh (Table 9.2).

The concentration of arsenic in rice considered to be safe ranges from 82 to 202 μg (Zavala & Duxbury, 2008). In arsenic endemic area, rice is contaminated with arsenic. The extent of arsenic contamination depends on the amount of arsenic in soil and irrigated water. When a person in arsenic endemic area consumes arsenic contaminated rice along with arsenic-contaminated drinking water (4 L/day), including vegetables with a high arsenic content, is sufficient to cross the maximum allowable daily level (MADL) limit of 220 μg/day (Correl et al., 2006).

Table 9.2 *Daily consumption of rice per person in 2010.*

Country	Daily consumption (g/day)
China	251
India	208
Indonesia	414
Bangladesh	441
Vietnam	465
Myanmar	578
Thailand	285
Philippines	267

(Source: FAO)

Speciation of rice is also estimated. Inorganic arsenic and DMA dominate in raw rice (Zavala et al., 2008). The proportion of inorganic arsenic in total

arsenic in rice ranges from 11% to 93% (Torres-Escribano et al., 2008).

Our target is to reduce arsenic consumption through foodstuff in arsenic endemic area. Initial screening of foodstuffs for arsenic in arsenic endemic area is the first step.

There are currently no regulations that are applicable to inorganic arsenic in food in the USA and EU. Only China has set a regulatory limit in food at 150 μg per kg of rice. In October 2005, the Ministry of Health of China adopted a new food safety standard on arsenic in foods (Table 9.3). This standard, specified for a variety of food products, has been set for inorganic arsenic, and not for total arsenic. This is an important step as it recognizes that total arsenic in foods is not appropriate for evaluating food safety.

Table 9.3 *Chinese food safety standard for inorganic arsenic (mg/kg) in foodstuffs.*

Foodstuff	Inorganic arsenic (mg/kg)
Rice	0.15
Flour	0.10
Other cereals	0.20
Vegetables	0.05
Fruit	0.05
Poultry	0.05
Egg	0.05
Milk powder	0.25
Fresh milk	0.05
Beans pulses	0.10
Fish	0.10
Algae	1.50
Shellfish	0.50

A study shows the amount of arsenic in rice bought from markets in UK that had been grown in America, Europe, India, and Bangladesh. An average of 260 μg/kg arsenic was found in US rice. The rice imported from India showed a low

amount of 50 μg arsenic per kg, whereas from Bangladesh it was about 150 μg arsenic per kg.

The total arsenic content of 150 paddy rice samples collected from different areas of Bangladesh. Arsenic concentrations varied from 10 to 420 μg/kg at 14% moisture content. Rice yields and grain arsenic concentrations were 1.5 times higher in the boro rice (cultivated winter season) than the aman rice (during summer or monsoon season), consistent with the much greater use of groundwater for irrigation in the boro season. Mean values for the boro and aman rices were 183 and 117 μg/kg, respectively. The variation in arsenic concentrations in rice was only partially consistent with the pattern of arsenic concentrations in drinking water tube wells. Processing of rice (parboiling and milling) reduced arsenic concentrations in rice by an average of 19%. Human exposure to arsenic through rice would be equivalent to half of that in water containing 50 μg/kg for 14% of the paddy rice samples at rice and water intake levels of 400 g and 4 L/cap/day, respectively (Duxbury et al., 2003).

9.1.1 Raw and Cooked Rice

In Bangladesh, the raw rice is contaminated with arsenic with highest levels of 1.8 mg/kg (Meharg & Rahman, 2003) (Table 9.4). Although the amount of arsenic in rice varies that may be due to inadequate number of samples, area from which it is collected and method of estimation.

There are two varieties of rice: uncooked rice (atap chal; local language) and cooked rice (sidha chal; local language). Bangladeshi like to eat sidha chal. Sidha chal means the paddy rice, collected from the field, is cooked with water. Then it is dried. It is again cooked before intake as boiled rice. When the paddy is cooked with high concentration of arsenic contaminated water twice, once at the processing of rice and another just before intake as boiled rice (Misbahuddin,

2003), then there are more accumulation of external arsenic into the rice. This rice contains its organic acid and external inorganic arsenic. However, boiling of rice for 5 min will reduce the arsenic concentration by 20% and for 25 min the concentration will reduce by 65% (Chakravarty et al., 2003). Cooking may affect the intake of arsenic through foodstuff (Bae et al., 2002).

A rice sample (with undetectable amount of arsenic) showed arsenic in the cooked rice (bhat) when it was cooked with arsenic-contaminated water. The quantity of arsenic was higher when water and rice were cooked so that all the water was absorbed by the rice by the time it was well-cooked (Huq et al., 2006). Bangladeshi cook rice with more amount of water and when the rice was well-cooked, the liquid starch was decanted. This method is a better method to reduce arsenic in rice.

Cooked rice collected from households during the field survey showed concentrations of arsenic from 0.11 to 0.36 mg/kg (Huq & Naidu, 2003). Another study shows that the content of arsenic ingested by a person from cooked rice is 0.124 mg from 460 g of rice (Chakravarty et al., 2003).

Different strains of rice show different degrees of arsenic uptake, and arsenic levels in rice are affected by concentration in irrigation water and soils.

Table 9.4 *Amount of total arsenic in raw rice.*

Authors	Number of samples	Amount of arsenic (μg/kg)	
		Range	Average
Khan et al., 2007	84	65-1,824	878
Meharg and Rahman, 2003		58-1,830	496
Ali et al., 2002	12	50-1,520	480
Smith et al., 2006	46	46-1,110	358
Das et al., 2004	10	40-270	136

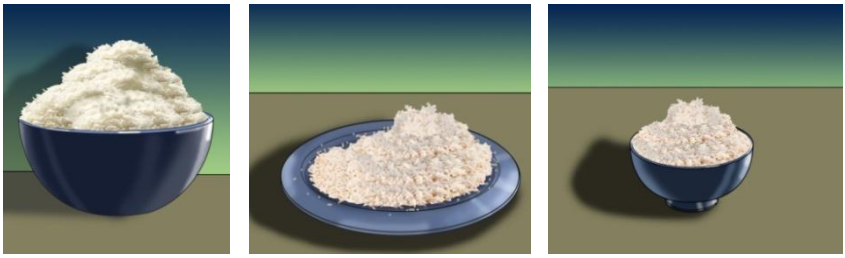

Figure 9.1 *Amount of rice in bowl in the past (left), in plate at present (middle) and in pot in future (right).*

Now the question is how to reduce the intake of arsenic through rice. There may be some suggestions. For example, three to four decades ago Bangladeshi preferred to eat bowl full rice (Figure 9.1). Now-a-days they prefer to eat plateful rice. In order to reduce the arsenic load, they should take potful rice. Total arsenic content of raw rice may be reduced 35 to 45% in cooked rice after rinse washing of raw rice and cook with high volume (6: 1, water: rice) of water (Raab et al., 2009). It may be adviceable to rinse rice in water until water runs clear. Then cook rice in excess water than usual. The diet should not be consumed every day. If possible, in the individual diet, rice should not be included every day. Everything depends on the motivation of people.

Arsenic is known to cause oxidative stress. On the other hand, rice contains hundreds of antioxidants. Although rice in arsenic endemic area has quite high amount of arsenic as well as antioxidants.

9.2 Vegetable

One of the important items of Bangladeshi dish is curry which contains a lot of water. If someone uses arsenic contaminated water, then there is chance of more intake of arsenic. Among the vegetables, leafy vegetables contain relatively low concentration of arsenic (Table 9.5). Potato contains low concentration of arsenic.

Table 9.5 *Speciation of arsenic in rice and vegetables from two arsenic-exposed areas of Bangladesh.*

Foodstuffs	*Local name*	*Number of samples*	*Speciation of arsenic in foodstuffs (µg/kg)*			
			Inorganic	*MMA*	*DMA*	*Total*
Raw rice	Chaal	75	296.3	222.5	363.4	882.2
Non-leafy vegetables						
Amaranth stem	Data	39	166.0	144.4	309.0	619.4
Arum stem	Kachur data	40	229.7	323.1	410.1	962.9
Dhundal	Dhundal	9	214.7	241.7	182.2	638.6
Egg plant	Begoon	42	252.6	191.6	449.1	893.3
Lady's finger	Dherosh	42	211.6	155.9	318.0	685.5
Papaya (green)	Kacha pepe	45	177.9	220.5	282.5	680.9
Pumpkin	Kumra	2	0	331.4	433.5	764.9
Ridge gourd	Jhingha	11	141.2	89.3	486.0	716.5
Snake gourd	Chichinga	22	270.3	121.6	294.7	686.6
Roots and tubers						
Taro	Kachur lata	34	377.6	232.3	533.5	1143.4
Arum root	Maan kachu	16	274.4	149.8	706.7	1130.9
		Leafy vegetables				
Amaranth leaf	Data shak	34	39.1	134.3	284.8	458.2
Arum leaf	Kachu shak	45	369.3	230.6	534.4	1134.3
Halancha leaf	Halancha leaf	22	196.0	130.2	348.1	674.3
Indian spinach	Pui shak	73	227.7	157.5	386.0	771.2
Jute leaf	Paat shak	10	212.1	98.4	321.8	632.3
Kalmi leaf	Kalmi leaf	3	62.3	0	49.2	111.5
Potato leaf	Alu shak	5	249.8	128.7	326.5	705.0
Pumpkin leaf	Kumra shak	26	225.3	193.4	365.9	784.6

(Misbahuddin et al., 2007)

On the other hand, high concentration of arsenic is found in arum (Misbahuddin et al., 2007). Arum is a common vegetable in rural Bangladesh for easy to cultivate and available throughout the whole season. Several varieties of arum are available and different parts are usually consumed. The higher values of arsenic in arum may be due to the use of contaminated water from hand pump tube well for its cultivation in the home garden. More than 150 mg/kg of arsenic has been found to be accumulated in arum.

Vegetables (Green papaya, red amaranth, bottle gourd leaf, potato, ripe tomato, green chili, etc) that are growing in the garden and receiving irrigation with arsenic-contaminated water have significantly higher levels than those grown in unaffected areas (Chakravarty et al., 2003).

Williams et al. (2006) analyzed total arsenic in vegetables, roots and tubers, pulses, and spices and found values up to 1.59 mg/kg dry weight in fruit vegetables and 0.79 mg/kg dry weight in leafy vegetables.

In an arsenic endemic area, it is impossible to eat any vegetable after estimating its arsenic level. Some vegetables like arum may be avoided. In reality, it is difficult to avoid the intake of arum by the poor Bangladeshi leaving in rural arsenic endemic area.

There are some vegetables which have compound(s) that can reduce the body arsenic load. These vegetables are amaranth and spinach. Corn also contains compound that can reduce arsenic in arsenic loaded rats. People in arsenic endemic area may be encouraged to eat these vegetables.

9.3 Soup

Liquid pulse is very popular in India and Bangladesh. They include it in their dietary manu every day. Pulse retains about 91.2% of arsenic when cook in arsenic contaminated water.

9.4 Salad

Green leafy vegetables are preferred by the Bangladeshi as salad. These are usually containing low amount of arsenic.

We cannot avoid the intake of rice instead encourage the people of endemic area for low intake of rice. The total calorie can be replaced by shifting the diet habit of potato, maize, etc.

9.5 Fruits

Arsenic was detected in all juices available in USA market. 32% demonstrated arsenic levels are nearly at or above the drinking water exposure limit of 10 ppb.

On a dry weight basis, some vegetables have much higher levels of arsenic than rice. However, a typical Asian diet includes much more rice than vegetables, so intake from rice remains the principal arsenic exposure through food.

Meanwhile, in a bid to reduce the amount of arsenic taken up by rice, researchers are attempting to design rice plants that do not absorb as much arsenic.

The proportion of inorganic arsenic ingested through food may be significant, even when the arsenic concentration of drinking water is higher than 50 ppb. For example, a recent study conducted in Mexico, where the concentration of arsenic in drinking water was as high as 400 ppb, found that even so 30% of inorganic arsenic intake came from food (DelRazo et al., 2002).

In conclusion, people of arsenic endemic area must change the food habit in order to reduce intake of arsenic from foodstuffs. For example, Bangladeshi must change their diet manu like combination of rice (small amount), chapati, dal, vegetable, boiled corn, boiled bean, and yogart (Figure 9.2). In 1960's, Koreans ate 600-800 g of cooked rice per meal. Korean has changed their dietary contents.

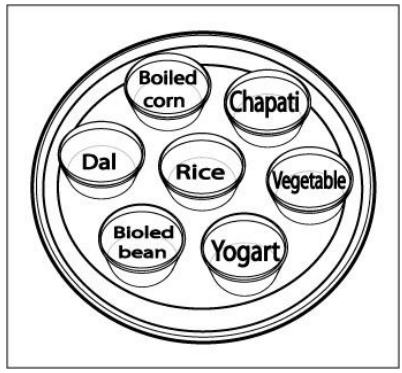

Figure 9.2 *Dietary manu for Bangladeshi.*

9.6 Questions to be Raised

1. In an arsenic endemic area, the arsenic contaminated hand pump tube wells are marked with red color in order to encourage the people not to drink that water. What measure can be taken in case of arsenic contaminated foodstuff?

2. Unlike water intake, it is not possible to estimate the arsenic content of any food before intake.

3. Most of the epidemiological studies show a close relationship between arsenic intake through water and the development of symptoms. So, is there any role of arsenic from food source?

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✶ Myth

Do not eat shrimp/prawn when taking 'vitamin C'.

Chapter

10

〖Management of Arsenicosis〗

Still now there is no effective treatment of arsenicosis. Even then, scientists and physicians are trying to relieve the symptoms of arsenicosis by reducing body arsenic load as well as complications. Body arsenic load can be reduced by a) stoppage of drinking arsenic contaminated water; b) intake of low arsenic contaminated food; c) avoid inhalation of arsenic contaminated air; and d) take drug that enhances biotransformation and excretion of arsenic. It is always advisable to start the treatment as soon as possible.

Animal model is important to findout an effective drug. However, it is a difficult task to make an animal model of skin manifestations of arsenicosis. Most of the animal studies show the effect of drug in reducing the body arsenic load as well as the evidence of oxidative stress. It has been tried to have animal

model of arsenic-induced cancer.

Only a limited number of studies conducted on human. Some studies are well designed whereas others are not. Based on these limitations, some of the antioxidant vitamins and minerals are suggested to be effective in the treatment of arsenicosis. The use of antioxidant is due to the development of arsenic-induced oxidative stress.

The administration of 1 g of sodium thiosulfate orally or intravenously causes a rapid and pronounced increase in the excretion of arsenic. Its use was first introduced by Paul Who is the Reader?

Doctor working in the arsenic endemic area will be the reader of this book.

(Ravaut, 1920). The oral administration of sodium thiosulfate (20 and 40 g) significantly decreased the arsenic load in milk, urine, and hair of cattle in arsenic endemic area after 1 month of treatment (Ghosh et al., 2011). It can also be administered intravenously and has adverse effects like nausea, joint pain, muscle cramp, blurred vision, agitation, and hallucinations.

The use of chelating agents like dimercaptosuccinic acid (DMSA), 2, 3-dimercapto-1-propanesulfonate (DMPS), dimercaprol (British anti-Lewisite; BAL) and d-penicillamine is effective in acute arsenic poisoning. However, their role in the treatment of arsenicosis remains inconclusive due to inadequate studies on patient. Major drawbacks of dimercaprol include (a) its low therapeutic index, (b) its tendency to redistribute arsenic to brain and testes, for example, (c) the need for intramuscular injection which is painful and (d) its unpleasant odor. When compared to dimercaprol, DMSA, DMPS were of significant lower toxicity and could be administered orally or intravenously (Aaseth, 1983). A well-designed study using DMSA shows its ineffectiveness in the treatment of arsenicosis (Guha Mazumder et al., 1998). The same

research group conducted another study which shows significant improvement in the clinical score of patients suffering from arsenicosis by administering DMPS (Guha Mazumder et al., 2001). This effect may be due to increased urinary excretion of arsenic during the period of therapy.

10.1 Non-malignant Skin Manifestations

Treatment of melanosis: Stoppage of drinking arsenic contaminated water is effective in the treatment of melanosis. However, it recurs when a patient starts to drink arsenic contaminated water again. In some of the arsenic endemic areas, almost all the hand pump tube wells are contaminated with high concentration of arsenic. In that situation, it is difficult to provide arsenic safe drinking water. In addition, the emphasis should be given on the provision of a diet rich in protein and vitamins. Intake of pleanty of grean leafy vegetable is advised.

Chronic Arsenicosis of Cattle in West Bengal and It's Possible Mitigation by Sodium Thiosulfate.

Treatment of keratosis: Stoppage of drinking arsenic contaminated water or shifting of highly arsenic contaminated hand pump tube well to low arsenic contaminated hand pumped tube well is necessary. Keratosis present in the palm and sole can be treated by topical application of salicylic acid with or without urea, propylene glycol, and neem. Orally administered compounds are beta-carotene, retinoid, ascorbic acid, alpha-tocopherol, zinc, selenium, spirulina, alpha-lipoic acid, and folic acid. These are not specific and require longer time to relieve (3-14 months). Among the vegetables, ceraels and spices that can be used include: spinach, corn, amaranth leaf, garlic, curcumin and kala jeera oil. Root of water hyacinth is also found to reduce the arsenic load in rat. The use of probiotics is also tried to find out its effectiveness in keratosis.

Salicylic acid: Salicylic acid is a keratolytic (peeling agent). It causes shedding of the outer layer of skin. The topical use of 10% boric acid ointment containing 6% salicylic acid in arsenical keratosis for treatment purpose has a long history (Hall, 1946). There was confusion about the percentage of salicylic acid that can be used in arsenical keratisis. Therefore, a randomized control trial on 150 cases with severity of disease (mild, moderate and severe), concentration of salicylate (5, 10, 20 and 30%), and duration of treatment (1, 3 and 6 months) was conducted (Islam et al., 2007). Almost all cases of mild and moderate forms of keratosis were found to be improved (97.6 and 95.0% respectively) whereas severe cases showed comparatively less improvement (67.5%). About 90% improvement was observed using 20 or 30% concentration in mild keratosis within 1 month and 100% improvement with 10, 20 or 30% concentrations within 3 months of treatment. In the case of moderate keratosis, more than 90% improvement was found using 5% concentration or more after 6 months of treatment. More than 90% improvement was noted in the severe form of keratosis only by using 30% concentration salicylic acid for 6 months. For simplicity, it is recommended to use 20% salicylic acid for keratosis.

Urea: The urea is an emollient (that is, skin softening agent). It helps to moisturize the skin. The use of urea with salicyclic acid is suggested to treat arsenical keratosis. However, salicylic acid should not be used with urea (10-50%). The urea enhances the penetration of salicylic acid and produces the systemic adverse effects of salicylate.

Propylene glycol: Propylene glycol is usually used as a dissolving media for pararcetamol. A randomized study was conducted on 60 patients of arsenical palmer keratosis treated topically with three different concentrations (15, 30 and 45%) of propylene glycol once daily at both palms at bedtime for eight weeks (Dina & Misbahuddin, 2010). Thirty percent or more concentration of

propylene glycol was effective for mild to moderate form of keratosis. Propylene glycol was well tolerable. Both roughness and thickness of arsenical palmer keratosis can be reduced using propylene glycol and as the concentration of the drug increases, its effectiveness is increased without any significant adverse effect. Therefore, 45% proplylene glycol is recommended for topical use in the treatment of arsenical keratosis.

Neem: Neem is a plant which is extensively used in different diseases. Topical application of dichloromethane extract of neem (*Azadirachta indica*) once daily (overnight) for 12 weeks showed significant improvement in palmar arsenical keratosis (Ferdous and Misbahuddin, 2014). So, topical application of neem extract may be recommended for the treatment of arsenical keartosis.

Vitamin A: The serum concentration of retinol in patients with non-malignant skin lesions is not significantly changed from the control (Chung et al., 2006). However, oral administration of vitamin A (150,000 units) daily for three months was effective in arsenical keratosis following medicinal use of arsenic (Hall, 1946). Open clinical trial on arsenicosis shows its effectivenesss when combination of vitamin A, C and E were used.

The main disadvantage of using vitamin A is the longer duration of treatment. The effectiveness of vitamin A does not mean that the patient of arsenical keratosis has avitaminosis, hypovitaminosis or dysvitamino-sis.

Acitretin: Acitretin is a second generation retinoid. Combination of low dose acitretin and salicylic acid (16.7%) was also found to be effective (Son et al., 2008).

Beta-carotene: beta-Carotene is the precursor of vitamin A. The serum concentration of beta-carotene in patients with non-malignant skin lesions in West Bengal (India) is not significantly changed from the control (Chung et al.,

2006). However, patients of arsenic-induced skin cancer in Taiwan have low level of beta-carotene in blood (Hsueh et al., 1997). beta-Carotene was used with vitamin A, C and E for the treatment of non-malignant skin lesion. However, prolonged use of beta-carotene was found to develop lung cancer. A total of 29,133 male smokers 50 to 69 years of age from southwestern Finland were randomly assigned to one of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta-carotene, or placebo. The study was follow-up for five to eight years. Total mortality was higher among the participants who received beta-carotene than among those who did not (The alpha-tocopherol beta-carotene cancer prevention study group, 1994). beta-Carotene supplementation at pharmaco-logic levels may modestly increase the incidence of lung cancer in cigarette smokers (Albanes et al., 1996).

Selenium: Once arsenic was used to treat selenium poisoning in domestic animals. Nowadays, selenium is tried to treat arsenicosis. The dose and duration are important for selenium. Low dose may not produce any effect whereas excessive dose may cause selenium toxicity. In addition, longer duration of treatment is required (up to 14 months). One study shows that supplementation with L-selenomethionine for 6 months shows slight improvement in non-malignant skin lesions in patients, although the improvement was not statistically significant (Verret et al., 2005). Selenium reduces the oxidative damage and oxidative stress related gene expression in rat liver under chronic poisoning of arsenic (Xu et al., 2013).

Ascorbic acid: Isolated liver tissues of rat were first loaded with arsenic within the test tube at 37 ℃ and then treated with ascorbic acid (20 μg/mL) (Saha, 2006). The amount of reduced glutathione in normal liver tissue was 52.0 ± 0.2 μg/g protein. Addition of arsenic to the tissues reduced the amount of

GSH to 11.5 ± 0.3 μg/g protein. But when the arsenic loaded liver tissues were incubated with ascorbic acid, the amount of GSH was 14.2 ± 0.1 μg/g protein (22.6% increase; $p<0.001$). This study suggests that ascorbic acid increases the GSH level in arsenic-treated rat's liver. However, chronic intake of ascorbic acid may cause stone formation in the urinary tract.

Alpha-tocopherol: The serum concentration of alpha-tocopherol in patients with non-malignant skin lesions is not significantly changed from the control (Chung et al., 2006). However, serum concentration does not reflect the tissue concentration. There is 3-fold increased secretion of vitamin E from the skin of chest and back of arsenicosis in comparison to control or arsenic exposed individual (Yousuf et al., 2011). Chest and back skin are important sites of non-malignant skin lesions. A study on the vitamin E levels in the buccal cells of patients shows significantly low concentration in comparison to healthy volunteers. This low level of vitamin E in patients returned toward normal levels following supplementation with vitamin E (200 IU) caplet for 20 weeks (Misbahuddin & Farha, 2013). Supplementation with alpha-tocopherol for 6 months shows slight improvement in non-malignant skin lesions, although the improvement was not statistically significant (Verret et al., 2005).

A study conducted in southwestern Finland shows that alpha-tocopherol had no apparent effect on total mortality, although more deaths from hemorrhagic stroke were observed among the men who received this supplement than among those who did not (The alpha-tocopherol beta carotene cancer prevention study group, 1994).

A significant increase in the levels of protein oxidation, DNA strand breaks, and DNA-protein cross-links was observed in blood, liver, and kidney of rats exposed to arsenic (100 ppm in drinking water) for 30 days (Kadirvel et al., 2007). Co-administration of ascorbic acid and alpha-tocopherol to arsenic-exposed rats

showed a substantial reduction in the levels of arsenic-induced oxidative products of protein and DNA.

Vitamin E ameliorates arsenic-induced toxicities in the liver and kidney of mice (Verma et al., 2004).

Alpha-lipoic acid: In vitro experiment with small pieces of isolated liver tissue of rats incubated first in presence of arsenic and then with different concentrations of α-lipoic acid during the second incubation showed decreased amount of arsenic and malondialdehyde as well as increased the reduced glutathione level in dose dependent manner (Noor-E-Tabassum, 2006). These results suggest that α-lipoic acid remove arsenic from arsenic-loaded isolated liver tissues of rat.

Zinc: Rats were initially allowed to drink high concentration (400 μg/kg/day) of arsenic for two months followed by a period of cessation (one month) (Kamaluddin & Misbahuddin, 2006). Then the effect of zinc (2 mg/kg/day) in the removal of accumulated arsenic from differ-ent tissues (liver, kidneys, spleen and lungs) was examined. In arsenic-treated rats, the mean (± SD) amounts of total arsenic in liver, kidneys, spleen and lungs were 12.3 ± 0.7, 20.5 ± 1.0, 31.4 ± 1.0 and 25.6 ± 1.1 μg/g of tissues respectively. Administration of zinc to arsenic-treated rats reduced the arsenic concentrations of those tissues to 7.8, 10.7, 23.0 and 14.0 μg/g of tissues. This *in vivo* study suggests that zinc removes the accumulated arsenic from different tissues significantly ($p<0.001$).

Chronic intake of arsenic led to several folds higher secretion of zinc both in arsenicosis and arsenic-exposed controls than the healthy controls (Yousuf et al., 2011). The amount of zinc from the abdomen was similar in arsenicosis and arsenic exposed controls. Arsenicosis had higher level of zinc than that of arsenic-exposed controls in chest (15.6 ± 6.9 vs. l2.1 ± 9.0 μg/inch^2/24 hours)

and back (12.6 ± 5.4 vs. 9.0 ± 6.0 μg/inch^2/24 hours). The differences between the patients and arsenic-exposed controls were not statistically significant. The secretion of one molecule of arsenic was accompanied by secretion of two molecules of zinc.

Zinc consumed during the perinatal period of pregnancy can ameliorate the possible toxicities of arsenic exposure in the offspring by acting as an ameliorative supplement (Ahmad et al., 2013).

Folic acid: Folic acid plays an important role in the biotransformation of arsenic. Arsenic is methylation to MMA and DMA by a folate-dependent process. People having polymorphisms in certain genes involved in folate metabolism excrete low amount of DMA in urine, which may influence susceptibility to arsenic toxicity. A double-blind study in a population with low plasma folate observed that after 12 weeks of folic acid supplementation, the proportion of total urinary arsenic excreted as DMA increased and blood arsenic concentration decreased (Kile & Ronnenberg, 2008).

A study conducted on arsenic-treated rats (700 μg/day by gavage for 28 days) showed accumulation of arsenicin liver, kidney, heart, lung and skin which was significantly lowered ($p<0.05$) by both the folic acid and tetrahydrofolate (Rahman & Misbahuddin, 2010). Folic acid was found to be more efficacious compared to tetrahydrofolate.

Two hundred arsenic exposed adults with low plasma folic acid level showed significantly increased excretion of DMA in urine in comparison to control following folic acid supplementation of 0.4 mg/day for 12 weeks (Gamble et al., 2006). Folic acid can cause adverse-effects like depression, nausea, vomiting and skin rashes. It is, therefore, important to determine the correct dose and course length of folic acid in order to avoid adverse effects.

There role of folic acid in the treatment of arsenicosis is not yet studied.

Garlic: Twenty patients of mild to moderate degree of arsenical palmer keratosis were treated with garlic oil in soft capsule (10 mg) daily orally for 12 weeks (Misbahuddin et al., 2013). The mean (± SD) clinical scoring of patients before treatment was 102.8 ± 19.0. It was reduced to 36.0 ± 8.7 after completion of treatment (65% reduction). The mean amounts of total arsenic in nail of patients and arsenic exposed controls were 13 to 14-fold higher in comparison to healthy volunteers. Treatment with garlic oil reduced about 50% of the total arsenic accumulated in nails. Common adverse effects were garlic smell and gastric irritation. Oral administration of garlic oil improves symptom of arsenical palmer keratosis with reduction in body arsenic load.

Spirulina: Spirulina is blue-green algae. It is considered as superfood. Spirulina is available in the market for the treatment of several diseases. A placebo-controlled double-blind study was conducted to evaluate effectiveness of spirulina extract (250 mg) plus zinc (2 mg) twice daily for 16 weeks in the treatment of 24 cases of arsenicosis (Misbahuddin et al., 2006). The concentrations of total arsenic in water (without filtration) of placebo-and spirulina extract plus zinc-treated groups were 150.1 ±18.3 and 161.7 ± 23.9 mg/L, respectively. Intake of these high concentrations of arsenic lead to increased excretion of arsenic in urine (72.1 ± 14.5 mg/L in placebo-treated group and 78.4 ± 19.1mg/L in spirulina plus zinc-treated group). After 2 weeks of using filtered water, there were significant reduction of both arsenic intake through water and urinary arsenic excretion (8.3 ± 3.6 mg/Land 18.4 ± 7.3 mg/L in placebo group; 9.7 ± 5.4 mg/L and 21.6 ± 5.8 mg/L) in spirulina extract plus zinc-treated group. There was a sharp increase in urinary excretion of arsenic (138 ± 43.6 mg/L) at 4 weeks following spirulina plus zinc administration and the effect was continued for another 2 weeks. Spirulina extract plus zinc

removed 47.1% arsenic from scalp hair. Spirulina extract had nomajor adverse effect that required physician's attention. In spirulina extract plus zinc-treated group, the clinical scores for keratosis before and after treatment was statistically significant ($p<0.05$). Results showthat spirulina extract plus zinc may be useful for the treatment of arsenicosis with keratosis.

Corn: Water extract of corn reduced the amount of arsenic in different tissues of rat after exposure to arsenic (700 μg/rat/day) orally for 15 days (Chowdhury et al., 2009). Maximum reduction of arsenic occurred in liver (69.1%), kidneys (65.0%), lungs (63.5%), heart (57.6%) and skin (69.3%) and elevation of reduced glutathione level in all tissues (17.0% in liver, 46.7% in lung, 32.7% in heart and 55.4% in skin) except kidneys. This study suggests that corn extracts might protect rats from accumulation of arsenic in different tissues and oxidative stress, which is reflected by the increasing reduced glutathione concentration in those tissues.

Spinach: Hexane extract of spinach (1-4%) was effective in the removal of arsenic from arsenic-treated rat (Umar, 2007). Rats were fed arsenic trioxide through Ryle's tube for one month then they were fed on hexane extract of spinach for another one month. Hexane extract of spinach decreased accumulated arsenic from rat liver, spleen, kidney, intestine, lungs and skin significantly. Besides, it reduced the oxidative stress caused by arsenic which was evident by decreased levels of malondialdehye in the above tissues. Hexane extract decreased both arsenic level and MDA level in rat tissues in dose dependent manner, which was more effective at lower doses.

Roots of water hyacinth: Intraperitoneal injection of ethanol extract (dose: 50%) of water hyacinth for two days showed maximum arsenic lowering effect from different tissues of arsenic-treated rats (administered orally 500 μg/rat/day for 7 days) (Quayum, 2007). Besides, it reduced the oxidative stress caused by

arsenic, which was evident by decreased levels of malondialdehyde in tissues.

Curcumin: Curcumin is obtained from turmeric (popular South Asian spice) has its antioxidant and antimutagenic activity (Biswas et al., 2010). Blood samples taken from arsenicosis showed notable DNA damage and depleted antioxidant activity. Following dosage with curcumin capsules for three months, the DNA damage was reduced, ROS generation and lipid peroxidation was suppressed, and the antioxidant activity of blood plasma was raised. Arsenic-induced oxidative stress, apoptosis and alterations in testicular steroidogenesis and spermatogenesis in Wistar rats are ameliorated by curcumin (Khana et al., 2013).

Nigella sativa (Kala jeera): The oral administration of *N. sativa* oil (500 mg) capsules twice daily for 8 weeks is affective for the clinical improvement of palmar arsenical keratosis which is reflected by decreasing total arsenic load in nail as well as mean clinical scoring (Basher et al., 2014). Exact mechanism of effect is not known. However, there is protective effect of thymoquinone of *Nigella sativa* origin against arsenic-induced testicular toxicity in rats (Fouad et al., 2014).

Methionine: Arsenic consumed through drinking water may be quickly excreted from the body through methylation in the body through mostly urine. This methylation reaction needs methyl donors coming from food sources and it competes with normal metabolic processes. If body has enough supply of certain nutrient components like methionine, the toxic effects of arsenic are much reduced.

Green and black tea: Both teas afford efficient reduction of As^{III}-induced DNA damage in human lymphocytes (Sinha et al., 2007). It also quenched the excessive production of reactive oxygen species by arsenic, reduced the

elevated levels of lipid peroxidation, and increased the activity of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase). Furthermore, tea enhanced recovery of DNA damage, which was indicative of repair as confirmed by unscheduled DNA synthesis and pronounced expression of DNA repair enzyme poly (ADP-ribose) polymerase.

Probiotics: After 12 weeks supplementation with one capsule of probiotics (*Lactobacilli bugaicus* and *Bifidobacterium*), both E. coli count and stool arsenic level were significantly increased in patients (Rashid et al., 2014).

Co-administration: A study using rats showed that oral administration of zinc (1 mg/kg body weight/day) for 1 month is effective in the prevention of arsenic accumulation in different tissues such as spleen, lungs, kidneys, intestine and skin. But simultaneous administration of zinc and arsenic increased the accumulation of arsenic in different tissues particularly kidneys and spleen (Misbahuddin & Kamaluddin, 2002). The cause of which is not known but there may be enhanced absorption of arsenic by zinc. Simultaneous administration of selenium and arsenic enhanced the accumulation of arsenic in different tissues of rat (Nasir et al., 2002). Ascorbic acid enhances arsenic trioxide-induced cytotoxicity in multiple myeloma cells (Grad et al., 2001).

In case of spirulina, it takes months whereas in case of vitamin E, it takes 14 months treatment. This prolong treatment influences treatment cost and adherence. In addition, stoppage of drug intake reappears the symptom. Intake of beta-carotene or retinol may cause lung cancer. Simultaneous administration of zinc, selenium or manganese with arsenic may enhance the accumulation of arsenic in tissues.

10.2 Peripheral Vascular Disease

Peripheral vascular disease associated with gangrene is treated with drugs like pentoxyphyllin or calcium channel blockers with limited effect. Most of these patients need surgical amputation.

10.3 Peripheral Neuropathy

Tricyclic antidepressants such as amitryptiline may have utility in relieving painful dysethesias of arsenical peripheral neuropathy (Wilner & Low, 1993).

10.4 Respiratory Symptoms

In chronic bronchitis with or without obstruction, it is extremely important that bronchial irritation be reduced to a minimum. Smoking habits and dusty and smoke-laden atmospheres are to be avoided, and respiratory infection should be treated promptly. Bronchodilators have a limited role in interstitial lung diseases.

10.5 Treatment Options for Bowen's Disease

Several points should be considered before chosing the treatment option of Bowen's disease. These are the size, number and site of lesion and cost. The treatment options of Bowen's disease are: a) drug therapy, b) cryotherapy, c) curettage and cautery, d) laser therapy, e) photodynamic therapy, f) radiation, and g) excision. Most of these therapies have the risk of recurrence. Follow-up after each therpy for at least 6 to 12 months are requird to evaluate the recurrance. These appear to have generally similar efficacy and recurrence rates with no single therapy being superior for all clinical situations.

Drug therapy includes acitretin, 5-fluorouracil, imiquimod and diclofenac. Acitretinis given orally whereas 5-fluorouracil, imiquimodand diclofena are applied topically.

Acitretin: Daily treatment of acitretin (1 mg/kg) orally for 10 months cures Bowen's disease (Yerebaken et al., 2002). Apparent improvement was visible after three months of treatment. The effectiveness of this drug was found only in one patient. Another patient did not show any effectiveness due to discontinue of the drug. It is readily absorbed from the gut and widely distributed with a plasma half-life of 2 days. It may cause nausea, itching, headache, dry, red or flaky skin, dry or red eyes, dry or chapped lips, swollen lips, dry mouth, thirst, hair loss, depression or acne. There may be the possibility of severe birth defects and should not be used by pregnant women or women planning to get pregnant within 3 years following the use of acitretin.

Patient may be treated with acitretin 25 mg daily (Watson & Creamer, 2003). At this dose the patient may respond well with considerable improvement in lesions, many of which have cleared completely.

5-Fluorouracil: 5-Fluorouracil is a pyrimidine analogue that is used topically to the affected site as 3% cream once or twice daily for 9 weeks in the treatment of cancer (Sturm, 1979). It may cause the skin to become red and inflamed before it gets better. It acts by interfering DNA synthesis via inhibition of thymidylate synthetase and subsequently cell proliferation. The common adverse effect is irritation with erosions and ulcerations that may last several weeks. The effectiveness of treatment is increased (up to 96%) when 5-FU is combined with other therapeutic approaches like pretreatment with erbium:YAG laser, cryotherapy, imiquimod and acitretin (Khandpur & Sharma, 2003).

Imiquimod: Imiquimod, an immunomodulator, is applied to the affected skin regularly as cream (5%) once daily for 16 weeks in the treatment of Bowen's disease (Rosen et al., 2007). It may cause the skin to become red and inflamed before it gets better. It is usually recommended for lesion of larger-diameter and in leg. Follow-up study shows that recurrence developed after 19 months.

Diclofenac: Diclofenac sodium is used as an analgesic. There is a report on two cases of Bowen's disease treated with 3% diclofenac gel twice daily for 80 to 90 days with no residual disease clinically and histologically (Dawe et al., 2005). The treatment is well-tolerated with mild inflammation after 6 weeks. There may be mild adverse effects like itching and dryness.

Cryotherapy: Liquid nitrogen is sprayed onto the affected skin to freeze it. This procedure of freeze-thaw cycles are done twice. Each freeze cycle is being maintained for 5-10 second after the formation of an ice ball to the intended margin. The procedure may be painful and the skin may remain a bit uncomfortable for a few days. The treated area may blister and weep. The patch will scab over afterwards and usually fall off within a few weeks, removing the affected skin.

Curettage and cautery: The affected area of skin is scraped away under local anesthetic and heat or electricity is used to stop any bleeding, leaving the area to scab over and heal after a few weeks. Curettage and cautery are superior to cryotherapy in the treatment of Bowen's disease, especially for lesions on the lower leg (Ahmed et al., 2000). The abnormal skin is cut out and stitches may be needed afterwards. It is not the best option if the patch is large or if there are several patches.

Laser therapy: Complete response of Bowen's disease of the digits by CO_2 laser with no recurrence in the 0.5 to 7.7 years follow-up was published in some

studies with good functional and cosmetic outcome.

Photodynamic therapy: A light-sensitive cream is applied to the affected skin and a laser is directed onto the skin four to six hours later, to destroy the abnormal cells. The treatment session lasts about 20-45 minutes. A dressing covers the area afterwards, to protect it from light. The most commonly used photosensitizers are 5-aminolevulinic acid or methyl aminolevulinate that are used topically. Various illumination sources, wavelengths of light, and dosing schedules have been used. Photodynamic therapy is well-suited for large lesions, multiple lesions, and poor-healing sites. The adverse effects are burning and stinging. There may be rarely observed adverse effects like erosions, ulceration, and hyperpigmentation hypopigmentation.

Radiotherapy: X-ray or grenz-ray radiation therapy may be given for poor surgical candidates or patients with multiple lesions. It should be avoided for lower extremity lesions due to impaired healing.

Excision: The surgical excision of Bowen's disease is one of the standard treatments especially for small and single, digital and perianal Bowen's disease (Neubert & Lehmann, 2008). A study conducted on perianal Bowen's disease shows that recurrence rate for wide excision, local excision and laser therapy is 23%, 53% and 80% respectively (treatment with radiotherapy was not included) (Marchesa et al., 1997).

10.6 Treatment of Skin Cancer

Beta-carotene: Individual who selects diet high in beta-carotene has a lower incidence of squamous cell carcinoma and basal cell carcinoma (Kune et al., 1992; Hsueh et al., 1997).

10.7 Other Cancers

Cancer in lungs, urinary bladder or liver is not very rare. In this case, excision of bladder cancer due to chronic arsenicosis can be curative. In advanced cases of these cancers and in cases of internal cancers, the treatment options are meager.

Surgical intervention in mild-to-moderate keratotic papules or nodules has not been widely tried. Those lesions with sudden increase in size, cracks, and bleeding; and those of Bowen's disease, basal cell carcinoma, squamous cell carcinoma need to be surgically excised at the earliest opportunity.

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Chapter

11

〖Counseling〗

"Water is life. You can refuse to provide food or money but you cannot refuse to give water".

Proverb

Counselling of people for public education and social movalization is an important aspect in arsenic endemic area. We should have sufficient authentic information about arsenic and arsenicosis before starting counseling. Knowledge should be shared between technical persons and affected people.

There is a common practice that Government denies or suppresses the information of arsenic contamination when it is first discovered (Ravenscroft et al., 2009). It is due to reliability of information; chance to develop penic among

the people, and lack of confidence to solve the problem. However, this type of ignorance does not protect people from arsenic contamination. Instead, delayed response increases avoidable morbidity and mortality.

A study conducted in Bangladesh after 5-6 years of detection showed that more than 60% of people have no idea about arsenic. It is necessary to motivate the people, what is arsenic? It is a poison present not only in water, but also in food and air. Actually it is present everywhere and does not produce any health problem until the concentration is high.

Who will be the target members for councelling? It will be better if all the members are included in counseling. But it is difficult in endemic area of highly populated, particularly in Bangladesh and West Bengal. In that case, it is better to do couselling the head of the family. Allow the people, who cannot read, to ask question about arsenic. In addition, counseling may be done at school or college level. Continue to educate children about the serious health risks of consuming arsenic contaminated water. Repeatation is information about arsenic and its consequent health effects are important.

Advice the patient and other family members not to drink arsenic contaminated water. This water is not useable for cooking purpose. The water of red marked tube well may be used for bathing, and washing utensils. Arsenic contaminated water should not be used to drink by cow, chiken or other household animals.

The level of arsenic in hand pumped tube wells was estimated by national testing campaign in Bangladesh. Subsequently the level of arsenic was never estimated. It is unfortunate. Periodic estimation of arsenic in tube well water is vital. Motivation of people is necessary for periodic check up of both red marked and green marked hand pumped and motor driven tube wells for the level of arsenic with the help of local government. Advice the people to take

mitigation option of using arsenic safe drinking water.

Like adult, arsenic is not safe for extreme of ages: child and elderly people. Expectant mother and lactating mother are not safe. Arsenic crosses the placental barrier and reaches the fetus.

Explain the people that arsenic and iron in water are not same problem. Arsenic is not a germ. It can not be killed by boiling the water.

Arsenicosis is not a contagious disease. Eating or sleeping with someone who has arsenicosis, a healthy person could be infected.

Dietary counseling is required. Avoid high arsenic contaminated food. Each patient needs to take plenty of green leafy vegetables containing vitamins. Intake of nutritious food is also beneficial for the patient. Supplementation of vitamin A, C and E tablets may be taken by the patient continuously daily for three months followed by drug holiday of one month. The amount of vitamins depends upon the age of the patient and severity of non-malignant symptoms. Intake of high concentration of vitamin may cause adverse effects.

People in arsenic endemic area are willing to walk a long distance to avoid exposure if the source for arsenic-free water is a hand pump tube well. If the source for arsenic-free water is surface water, however, people are less likely to walk a long distance to take avoidance measures (Aziz et al., 2006).

Persons with poor health may also find it inconvenient to travel a long distance to collect arsenic safe drinking water.

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✶ Myth 1

Arsenical keratosis is a contagious disease.

Mir Misbahuddin is Professor of Pharmacology in the Faculty of Basic Science and Paraclinical Science, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. He received his **MBBS** (1979) from the Mymensingh Medical College under The University of Dhaka, and **PhD** (1988) from The University of Tokushima School of Medicine, Tokushima, Japan. He joined as Associate Professor at the Institute of Postgraduate Medicine and Research, Dhaka in 1993 and was promoted to Professor in Bangabandhu Sheikh Mujib Medical University in 2001. His research interest is to find out the drug for the treatment of arsenicosis. In addition, he is conducting clinical trials and bioequivalence study. He is, currently, the editor of Bangladesh Journal of Pharmacology. He was the editor of Bangladesh Medical Research Council Bulletin, Bangladesh Journal of Physiology and Pharmacology, Teachers' Association Journal. His keen interest is in the field of both asynchronous and synchronous virtual pharmacology. In asynchronous teaching, a student can use the teaching contents from a website at anytime, from anywhere and several times. In the synchronous teacher, he is trying to arrange live lectures for students of Pharmacology at under – and post-graduate level from home and abroad. He edited six books on his subject.

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