Chapter

3

〖Clinical Manifestations and Complications〗

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

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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.

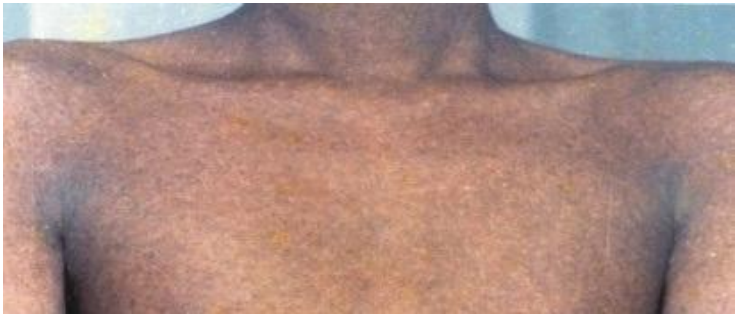

Figure 3.1 *Melanosis and leukomelanosis present in the skin of an arsenicosis individual (rain-drop appearance).*

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).

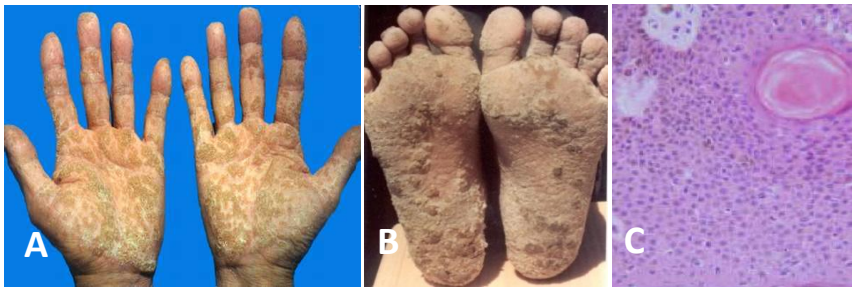

Figure 3.2 *Moderate arsenical keratosis at palms (A), severe form at soles (B) and the histological view (C) (Source: A and B were collected from the internet and C from the reference: An et al., 2004).*

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)

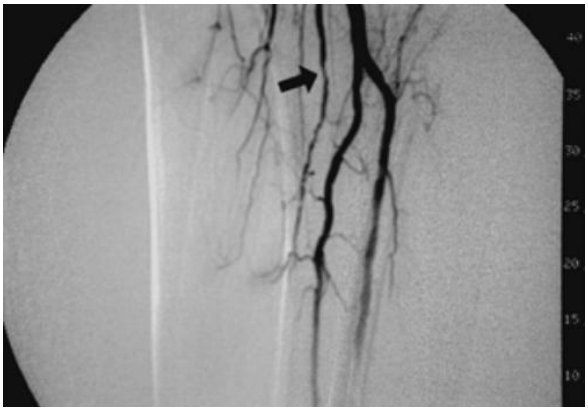

Figure 3.4 *Angiography of patient with blackfoot disease showed prominent occlusion of posterior tibial artery (arrow) with some collateral circulation (Yu et al., 2002).*

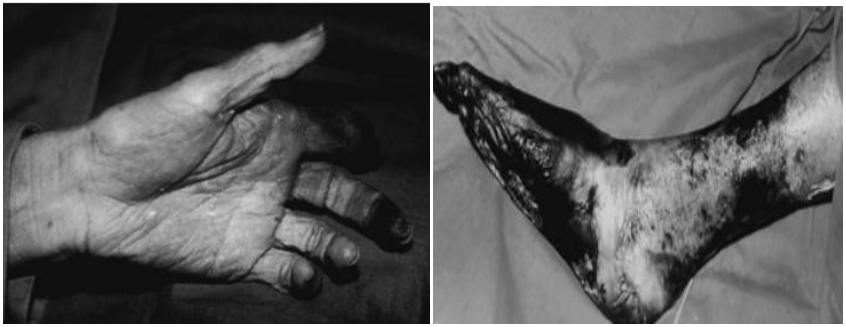

Figure 3.5 *Presence of blackfoot disease resulted in gangrene in hand (left) and leg (right) (Yu et al., 2002).*

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.

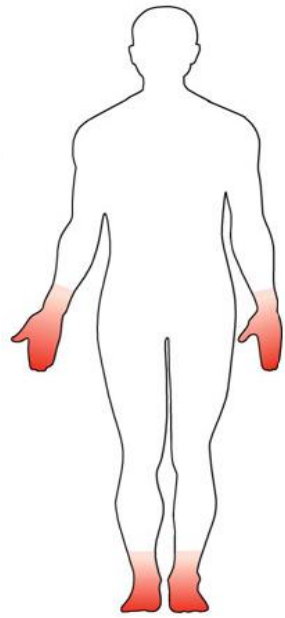

Figure 3.6 *Stocking-glove pattern of peripheral neuropathy (source: internet).*

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.

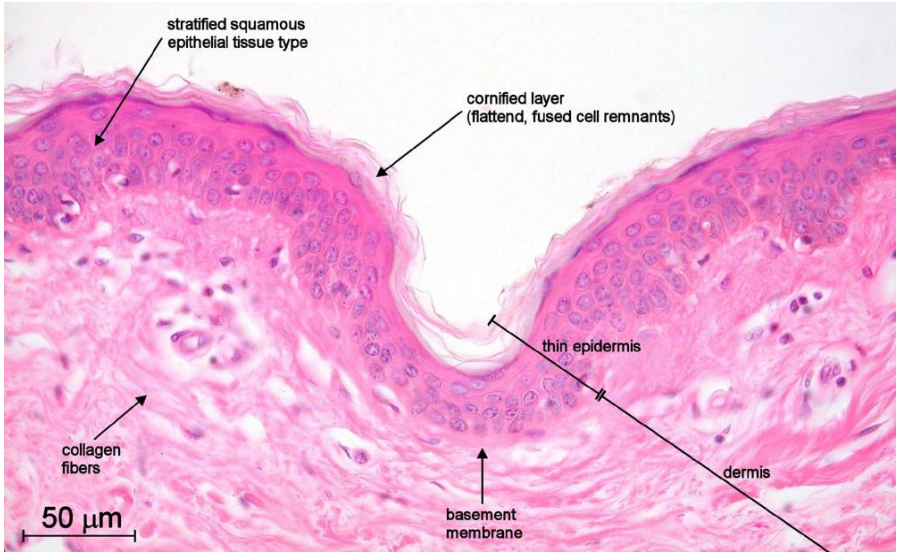

Figure 3.7 *Cross-section of the normal skin shown under microscope. Squamous cell carcinoma arises from the stratified squamous epithelial cells whereas basal cell carcinoma arises from the basal layer of keratinocytes (source: internet).*

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).

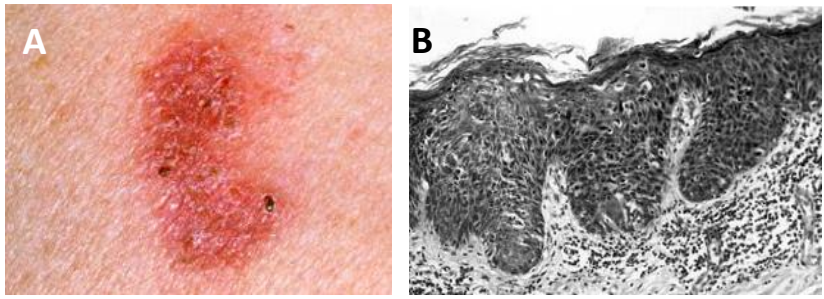

Figure 3.8 *Bowen's disease in skin due to chronic consumption of arsenic (A) and its histological appearance (B). The figure A is from the internet and the B from the reference: Centeno et al., 2002.*

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.

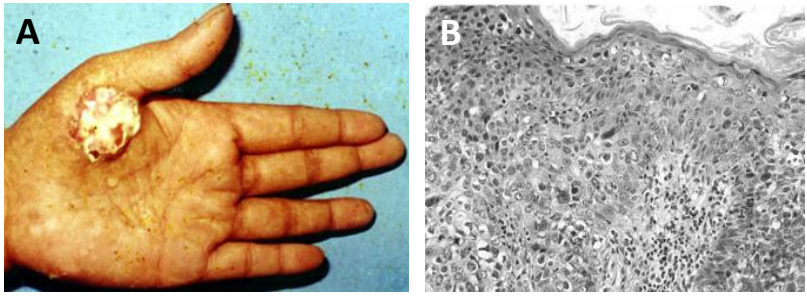

Figure 3.9 *Squamous cell carcinoma in hand due to chronic consumption of arsenic (A) and its histological appearance (B). A is taken from the internet (Courtesy from Arsenic Foundation) and B is taken from the reference: Centeno et al., 2002.*

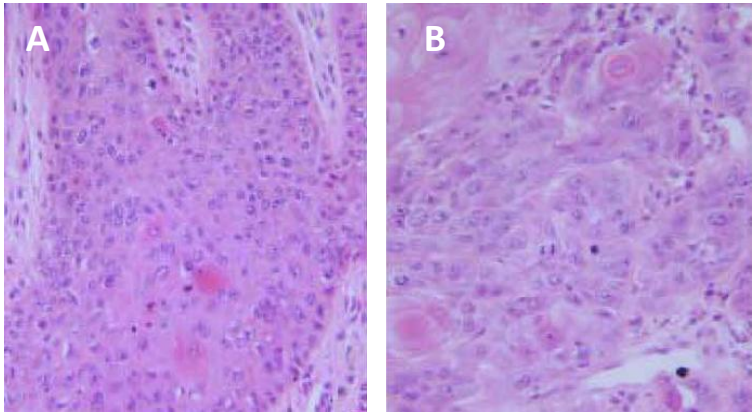

Figure 3.10 *Histological appearance of squamous cell carcinoma due to chronic consumption of arsenic (A) and non-arsenic related (B) (Centeno et al., 2002).*

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).

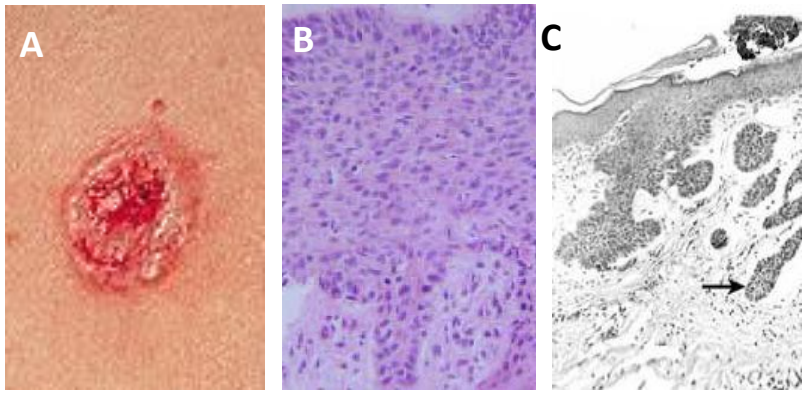

Figure 3.11 *Basal cell carcinoma in skin due to chronic consumption of arsenic (A) and its histological appearance (B: Centeno et al., 2002) and (C): An et al., 2004).*

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.

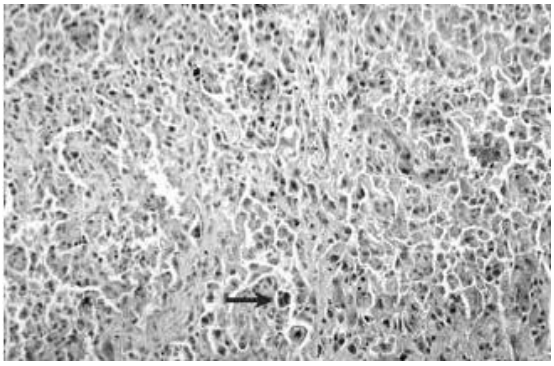

Figure 3.12 *Histological view of hepatocellular carcinoma. The nuclei are irregular, hyperchromatic, and occasionally multinucleated (see arrow).*

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

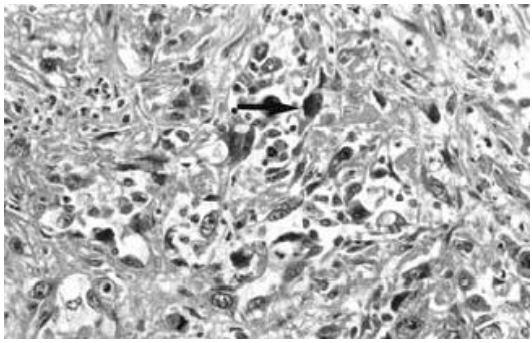

Figure 3.13 *Histological view of angiosarcoma of the liver.*

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.