

# A REVIEW OF ARSENIC POISONING AND ITS EFFECTS ON HUMAN HEALTH

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**ABSTRACT:** The incidence of arsenic contamination of ground water used for both irrigation as well as for human consumption or industrial activities has taken the dimension of an epidemiological problem. It has been established that inorganic arsenic is extremely toxic both acute and chronic. Initially it enters into the human body through ingestion, inhalation, or skin absorption. After entering into the body it is distributed in a large number of organs including the lungs, liver, kidney and skin. The clinical manifestations of arsenic poisoning are myriad, and the correct diagnosis depends largely on awareness of the problem. It is very difficult to diagnose early symptoms of arsenicosis because such non-specific symptoms may also be present in many other diseases. Medicine used for remedy of arsenicosis has been found to be unsatisfactory by repeated application and experience. Melanosis may disappear but keratosis is not altered; though it can prevent further complication. Once the

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complication (malignancy) has developed, using medicine may not prevent it. The symptoms and signs of arsenic poisoning may be reduced if the quality of drinking water were improved. Arsenic free water or decrease in arsenic level in the drinking water source is essential for overall development.

**KEY WORDS:** Arsenicosis, acute toxicity, chronic toxicity, melanosis, keratosis, cancer, ground water, remedy.

## **I. INTRODUCTION**

Arsenic is an element that raises much concern from the both environmental and human health standpoints. Humans may encounter arsenic in water from wells drilled into arsenic-rich ground strata or in water contaminated by industrial or agrochemical waste.<sup>62</sup> They may come in contact with arsenic in contaminated dusts, fumes, or mists. They may eat food contaminated with arsenical pesticides or grown with arsenic-contaminated water or in arsenic-rich soil.<sup>99</sup> In experience of one of us (KCS) food grown in arsenic affected areas arsenic is not found inside the food like cereals, pulses, fruits, but may be found in external layer of food or fruits due to spreneld of arsenicated water. Similarly milk of arsenic affected cows is free from arsenic due to modification inside body or some barrier action of unknown mechanism. A few stray reports of arsenic in cow's milk are most likely due to adulteration of milk by arsenicated water.

This element has long been associated with criminal activity and still is an emotionally highly charged topic, as large homicidal doses can cause cholera like symptoms (acute poisoning) and death. Ingestion of

low dose via food or water is the main pathway of this metalloid into the organism, where absorption takes place in the stomach and intestines, followed by release into the bloodstream. In chronic poisoning, arsenic is then converted by the liver to a less toxic form, from where it is eventually largely excreted in the urine. Only very high exposure can, in fact, lead to appreciable accumulation in the body. Minor alternative pathways of entry are known through inhalation and dermal exposure.<sup>20</sup>

Arsenic is a protoplasmic poison due to its effect on sulphhydryl group of cells interfering with cells enzymes, cell respiration and mitosis.<sup>55</sup> Chronic arsenical poisoning and medicinal use of arsenic are known since long. Arsenic was used orally as Fowler's solution in tonic mixtures and in the treatment of asthma, leukaemia and other malignancies.<sup>73, 141</sup> Parenterally arsenic was used in the past for the treatment of syphilis<sup>82</sup>, topical eosinophilia<sup>76</sup>, trepanosomiasis<sup>84, 88</sup>, Lichen planus, verruca planum and psoriasis.<sup>54</sup> Domestic, agricultural and industrial uses of arsenic<sup>23</sup> in the form of insecticides, weedicides, rodenticides and arsine are becoming rarer because of advent of low toxic pesticides. Chronic hepatitis and hepatic cirrhosis have been described due to consuming arsenic contaminated beer.<sup>108, 138</sup> Non-dermatological features of chronic arsenical poisoning by consuming arsenic contaminated drinking water were first reported in 1961 by Tseng et al., in Taiwan<sup>126</sup>, followed by Rosenberg<sup>109</sup> at Chile by Datta in India<sup>26</sup>. Saha's report<sup>112</sup> is the first report in world literature of chronic arsenical dermatosis from consuming arsenic contaminated tube well water.

Nowadays, it is generally acknowledged that different species of an element can exert diverse toxicological and biological effects in animal and human system.<sup>64</sup> This obviously also applies to compounds

whose toxicity greatly varies. The inorganic forms of arsenic exhibit the highest toxicity level<sup>40</sup>, while organoarsenicals are usually less toxic than the inorganic arsenic species. Indeed, some organic arsenic compounds, such as arsenobetaine (AsBet) and arsenocholine (AsChol), are well tolerated by living organisms<sup>41,101</sup>. From this point of view, it is becoming increasingly important that the various forms of arsenic be qualitatively and quantitatively determined in biological fluids and tissue as well as in matrices of nutritional and environmental relevance, especially in marine ecosystem. This will allow for a much better assessment of the risk associated with exposure to arsenic compounds.

Legal provisions are at present almost exclusively concerned with the total amount of the element in foodstuff and drinking water. According to the World Health Organisation (WHO), the provisional total daily intake should not exceed 2 ?g of inorganic arsenic per kilogram of body weight. Marine organisms are considered to be among the greatest bioaccumulators of arsenic due to given the tendency shown by this element to replace N or P in several compounds, thus producing AsBet, AsChol, algal arsenosugars etc., but they are harmless to the system.

## **II. SOURCE OF EXPOSURE**

Exposure to arsenic may come from natural source, from industrial source, or from administered i.e., accidental source. Self-administration of arsenic, unintentionally i.e., accidental consumption by children or deliberate i.e., homicidal or suicidal in attempts by adults, represents the rare causes of acute poisoning<sup>47</sup>. The source of such self-administration is typically an arsenic-containing insecticide, herbicide, or rodenticide. From a clinical perspective, massive exposures are now not usually seen in suicidal or homicidal setting;

accidental exposures, usually not serious yet largely preventable, are usually seen in children, and chronic or intermittent exposures often are the most diagnostically challenging. Exposure to arsenic via drinking water, air, food, and beverage has been reported occurring at many places in the world. Exposure through drinking water is increasing due to contamination from industrial operation and over withdrawal of groundwater for irrigation.

Occupational and environmental health problems can result from the frequent commercial presence of arsenicals. Exposure to arsine gas is also an environmental health hazard of concern in numerous occupational circumstances. Arsine is a colourless, odourless, tasteless, nonirritating gas that causes a rapid and unique destruction of red blood cells and may result in kidney failure, which is uniformly fatal without proper therapy. Most cases of arsine poisoning have occurred with the use of acids and crude metals of which one or both contained arsenic as an impurity.<sup>42</sup>

The two usual routes of absorption of arsenic are by ingestion and/or inhalation. There may be some degree of skin absorption of trivalent arsenic oxide since it is more lipid-soluble than the pentavalent form.<sup>137</sup> If the contact is by ingestion, then symptoms caused by acute gastrointestinal irritation will dominate the reaction. Ingested arsenic has a shorter half-life than inhaled arsenic due to more rapid biotransformation in the liver.<sup>132</sup> If the inhalation is the route of initial contact, then respiratory irritation will be a major determinant of early symptoms. However, once the arsenic is absorbed, the vascular circulation will ensue contact with a wide variety of potential symptoms reflecting the diversity of possible organ damages.

Arsenic enters the human body through ingestion, inhalation, or skin absorption. Most ingested and inhaled arsenic is well absorbed through the gastrointestinal tract and lung into the blood stream. 95 percent of the ingested trivalent arsenic is absorbed from the gastrointestinal tract. It is distributed in a large number of organs including the lungs, liver, kidney, and skin.<sup>63</sup> After absorption through lungs and the gastro-intestinal tract, 95 to 99 % of the arsenic is located in erythrocytes, bound to the globin of hemoglobin and is then transported to the other parts of the body. About 70% of the arsenic are excreted mainly through urine. Most arsenic absorbed into the body is converted by the liver to less toxic methylated form that is efficiently excreted in the urine. The rate of decrease of arsenic in the skin appears to be specially low compared with the rate for other organs.<sup>129,139</sup>

### **III. ARSENIC POISONING**

#### **A. Acute Poisoning:**

Symptoms of acute intoxication usually occur within 30 minutes of ingestion but may be delayed if arsenic is taken with the food. Initially, a patient may have a metallic taste or notice a slight garlicky odor to the breath associated with a dry mouth and difficulty in swallowing. Early clinical symptoms at acute arsenic intoxication may be muscular pain, weakness with flushing skin. Severe nausea and vomiting, colicky abdominal pain, and profuse diarrhoea with rice-water stools abruptly ensue. Capillary damage leads to generalized vasodilation, transudation of plasma, and vasogenic shock. Arsenic's effect on the mucosal vascular supply, not a direct corrosive action, leads to transudation of fluid in the bowel lumen, mucosal vesical formation, and sloughing of tissue fragments. The patient may complain of muscle cramps, numbness in hands and feet, reddish rashes in the body and intense thirst. In severe poisoning, the skin becomes cold

and clammy, and some degree of circulatory collapse usually occurs along with kidney damage and decreased urine output. Drowsiness and confusion are often seen along with the development of a psychosis associated with paranoid delusions, hallucinations, and delirium. Finally, seizures, coma, and death, usually due to shock, may ensue.

Following the gastrointestinal phase, multisystem organ damage may occur. If death does not occur in the first 24 hrs. from irreversible circulatory insufficiency, it may result from hepatic or renal failure over the next several days. Cardiac manifestations include acute cardiomyopathy, subendocardial haemorrhages, and electrocardiographic changes. The most common changes on an electrocardiogram are prolonged QT intervals and non-specific ST-segment changes.<sup>50</sup>

### **B. Chronic Poisoning:**

Chronic arsenic poisoning is much more insidious in nature, often involving multiple hospital admissions before the correct diagnosis is made. Arsenical dermatosis was rarely picked up from the variety of so many dermatosis. The source of arsenic exposure is discovered in fewer than 50% of cases. The most prominent chronic manifestations involve the skin, lungs, liver and blood systems. This was first diagnosed in West Bengal and Bangladesh patient of Khulna in December, 1984<sup>113, 114</sup> by Prof. K. C. Saha in July 1982 at School of Tropical Medicine, Calcutta.<sup>112, 113</sup>

The cutaneous changes are characteristic yet non-specific. An initial persistent erythematous flush slowly, over time, leads to melanosis, hyperkeratosis, and desquamation. The skin pigmentation is patchy

and has been given the poetic description of "raindrops on a dusty road". The hyperkeratosis is frequently punctuate and occurs on the distal extremities. A diffuse desquamation of the palms and soles is also seen. Long-term cutaneous complications include the development of multicentric basal cell and squamous cell carcinomas.<sup>103</sup> One of us (KCS) found mostly squamous cell carcinoma and Bowen's disease both monocentric and multicentric but Basal cell carcinoma was not found in skin out of 222 malignancies in arsenicosis.<sup>113, 114</sup> Bowen's disease, a rare precancerous skin lesion, is associated with both arsenic and human papilloma virus (HPV). Both arsenic and HPV cause cancer of the epithelial tissue<sup>79</sup>, and one may speculate that arsenic cause cancer in human beings through the activation of an oncogenic virus like HPV. This would explain why arsenic promotes cancer of the epithelial tissue in human beings but not in rodents, which normally do not carry papilloma virus.<sup>120</sup> Brittle nail, patchy alopecia, and facial edema are reported in the literature in arsenical skin diseases. One of us KCS<sup>113</sup> experienced non-pitting oedema of feet and rarely conjunctival congestion as additional signs in arsenical dermatosis (ASD).

Anaemia and leukopenia are almost universal with chronic arsenic exposure. Thrombocytopenia also frequently occurs. The anaemia is usually normochromic and normocytic and caused at least partially by haemolysis.<sup>67</sup> Interference with folate metabolism and DNA synthesis may result in megaloblastic changes.<sup>135</sup> In underdeveloped countries like India and Bangladesh, the presence of anaemia, leucopenia and thrombo cytopenia from arsenic are to be carefully assessed keeping in mind the common association of anaemia and leucopenia from malnutrition.

#### **IV. PRIMARY SYMPTOMS AND DIAGNOSIS OF ARSENIC DISEASES**

##### **Clinical Symptoms:**

Clinical symptoms occurring in the early stage of human arsenic poisoning were unspecific. The clinical manifestations of arsenic poisoning are myriad, and the correct diagnosis depends largely on awareness of the problem. Among the people who were taking high-arsenic water, early symptoms included, following non-specific symptoms, which can be present in many other diseases.

- ?? Palpitations
- ?? Fatigue
- ?? Headache, dizziness, insomnia, weakness
- ?? Nightmare
- ?? Numbness in the extremities, anaemia

##### **Stages of Clinical Features of Arsenic Toxicity**

Arsenical toxicity or arsenicosis develops insidiously after six months to two years or more depending on the amount of intake of arsenic laden ground water and arsenic concentration in the water. The higher the concentration above the maximum permissible level (0.05 mg/L) or higher the amount of daily water intake, the earlier the onset of symptoms.

The features of arsenical toxicity has been classified by Dr. Saha<sup>114</sup> which are now known as Saha's classification of stages. These are (1) Preclinical, (2) Clinical, (3) Internal complication and (4) Malignancy.

**1. Pre-Clinical (asymptomatic) Stage:** This may be subdivided into (a) Labile, chemical or **blood phase (transient)**. Urine showing arsenic metabolites, Dimethylarsonic acid (DMAA) and Trimethyl arsinic acid (TMAA) , during intake of groundwater containing high arsenic concentration; (b) Stable, sub-clinical or occult phase or **tissue phase (persistent)**. Body tissue showing high arsenic concentrations with no apparent clinical symptoms. *Blood phase (Labile):* After the intake of arsenic contaminated water, blood and urine examination reveals arsenic products but on withdrawal of it, urine becomes free of arsenic. The nature of arsenic revealed in urine is dimethyl arsonic acid (DMAA) and trimethyl arsinic acid (TMAA).

*Tissue phase (stable):* In this phase, examination of nails, hair and skin scales or other body tissues reveals high arsenic concentration, though the features of arsenic toxicity are absent. Unaffected members of an affected family often are in this stage.

**2. Clinical Stage (symptomatic or overt phase):** The presence of clinical symptoms is confirmed by detection of higher arsenic concentration in nail, hair and skin scales. Idea of skin scales for arsenic was also first observed by Prof. Saha.<sup>113</sup>

**Onset:** The features of arsenical toxicity appear gradually and slowly with time. Six month to ten years (average 2 years) may be required for the development of clinical features. If the arsenic concentration in water consumed is not very high or the daily water intake is low or if the patient spends most of the day in other unaffected areas for business or service or if the nutritional status of the patient is good, the clinical

features may not developed for years and if it develops at all, the sign are often mild. On the other hand if these conditions are not satisfied, the symptoms may develop between 6 months to 2 years.

### **Major Dermatological Signs:**

(i) **Melano-keratosis:** Melanosis i.e., dark pigmentation-diffuse and/or spotted keratosis i.e., dry, rough spotted nodules in palms and/or soles are the chief symptoms of arsenical dermatosis (ASD). It should be noted that there are various causes of melanosis and keratosis, spotted and diffuse, genetic and acquired. The combination of the two features-melanosis and keratosis-in the same patient in adults points to the diagnosis of arsenical dermatosis. Genetic disorders are often present since childhood and acquired diseases like arsenicosis appear in later life.

(ii) **Melanosis:** Diffuse darkening of skin starts in the palm and gradually spreads to the whole body (Photograph 1). Mild melanosis can be revealed by comparing with normal palm.

(iii) **Spotted or rain drop pigmentation (spotted melanosis)** is usually seen on chest, back or limbs. This is a fairly common symptom. (Photograph 2 shows a patient with severe spotted melanosis). 50% of the patients show spotted melanosis in chest, back and sometimes in the limbs, i.e., hands and legs.

(iv) **Spotted and Diffuse Keratosis** of palms and soles (Photograph 3) are signs of moderate to severe toxicity. Rough, dry, spotted nodules (spotted keratosis) appear after 5-10 years in the palms and feet. Still later (>10 years), the skin becomes dry and thickened . This stage is called diffuse keratosis. Gradually thickening of soles can give rise to cracks and fissures (hyperkeratosis).

(v) **Leucomelanosis** This observation was also made first by Dr. K. C. Saha. About one third of the

patients develop pigmented and depigmented spots in legs or trunk, found in advanced stage of the disease. Probably stimulation of melanocytes produces the pigmentation and damage in later stage is responsible for the depigmentation spots. Leucomelanosis is common ( white and black in colour) in persons with advanced arsenicosis or who have stopped drinking arsenic-contaminated water but had spotted melanosis earlier. (Photograph 4 shows such a case in Nadia district). **(vi) Dorsal keratosis** i.e., rough dry skin often with palpable nodules (spotted keratosis) on dorsum of hands, feet and legs are the signs seen in severe case (Photograph 5). If the arsenic intake is high or the disease is of long duration- more than 10-15 years- keratosis also develops in the dorsal skin of hands, feet, legs or even other parts of the skin (whole body keratosis).

**(vii) Combination of pigmentation (Melanosis) and nodular rough skin (spotted palmoplantar keratosis)** in post childhood age almost points to arsenic toxicity excluding other of causes of isolated pigmentation and keratosis (nodular rough skin), Palmoplantar skin was involved in early phase and keratosis of limbs in later phase.

#### **Minor Dermatological Feature:**

**(i) Mucus membrane melanosis** on tongue, gums, lips etc. may also be manifestations of arsenic toxicity.

In some cases pigmentation also appears in tongue, inner side of lips, gums or mucus membrane of mouth.

**(ii) Non-Pitting oedema:** In rare cases oedema appears in feet which does not pit on pressure without any history of attracts of pain or fever, differentiationship from filarial lymphoedema. This was also first

pointed out as an additional sign of arsenicosis by one of us KCS.<sup>113</sup>

**(iii) conjunctival congestion:** Sometimes observed (4%) as reddish eye due to conjunctival congestion without any sign of inflammation like grating sensation, pain or sticky discharge.

**3. Stage of Internal Complications:** In this stage, non-dermatological toxic features appear in addition to dermatological signs. The common complications are: Lungs, Asthmatic bronchitis (cough, expectoration, breathlessness, and restrictive asthma). Symptoms of clinical phase are associated with different complications as the other organs like lungs, liver, muscles, eyes, vessels are affected. Clinical symptoms are associated with bio-chemical evidence of organ dysfunction as well as histological, histochemical abnormalities and high concentrations of arsenic in different organ involved. Liver enlargement (hepatomegaly), spleen enlargement (splenomegaly) & fluid in abdomen ascites are seen in several cases.

**4. Stage of Malignancy:** Malignancy affecting skin, lungs, bladder uterus or other organs develops if patient survives the stage of complications. Malignancy does not develop before 10 years of arsenic exposure<sup>113</sup>. Usually after 15-20 years after the onset of first symptoms, cancer develops. Skin cancers are mostly monocentric but sometimes multicentric cases are also found. Usually they have slow progress for years. But sometimes in 6 months malignancy extends to neighbouring glands and in 9 months to 1-year time, patient often expires.

a) Skin, lungs, bladder, genito urinary tract etc.

b) Squamous cell carcinoma (Photograph No. 6), Basal cell carcinoma, Bowen's disease, Carcinoma

affecting lung, uterus, bladder, genitourinary tract or other sites are often seen in advanced neglected cases suffering from 10-20 years.

**Other Rare Signs:**

- (a) Arterial insufficiency (Blackfoot disease of Taiwan)
- (b) Mee's lines in nails

**V. TOXICITY OF ARSENIC TO HUMANS**

Most laboratory animals appear to be substantially less susceptible to arsenic than humans. It has been reported that chronic oral exposure to inorganic arsenic (0.05-0.1 mg/kg/day) causes neurological and haematological toxicity in humans but not in monkeys, dogs, and rats exposed to arsenite or arsenate at doses of 0.72 to 2.8 mg/kg/day.<sup>17</sup>

There is good evidence that arsenic is carcinogenic in humans if exposed orally or by inhalation, but not in animals. Therefore, quantitative dose-dependent data for animals should not be considered a reliable source to apply to humans.<sup>87</sup>

**A. Respiratory Effects:**

Effects of arsenic on the human respiratory system have been reported both from occupational exposure as well as from tubewell water arsenic toxicity. Humans exposed to arsenic dust or fume inhalation are more apt to be encountered in mining and milling of ores, in industrial processing, such as smelting industry which often produces irritation of the mucous membrane, resulting in laryngitis, bronchitis, rhinitis

and tracheobronchitis, causing stuffy nose, sore throat, hoarseness and chronic cough etc.<sup>27</sup> Very high exposure to unprotected workers may manifest perforated nasal septum after 1-3 weeks of exposure<sup>106</sup>, but such effects are minor or absent at exposure levels of 0.01-1 mg/m<sup>3</sup>.<sup>65</sup> A fatal case of arsenic trioxide inhalation manifested widespread tracheobronchial mucosal and sub mucosal haemorrhages with mucosal sloughing, alveolar haemorrhages, and pulmonary edema.<sup>48</sup> Chronic asthmatic bronchitis and asthma is a common complication of ground water arsenic toxicity<sup>113</sup>. No reports exist on the respiratory effects of organoarsenicals in humans.

## **B. Cardiovascular Effects:**

It has been suggested by several epidemiological studies that chronic inhalation of arsenic trioxide can increase the risk of death in humans from cardiovascular disease.<sup>4,70,133</sup> Long term inhalation of inorganic arsenic could injure the blood vessels or the heart. Zaldivar<sup>143</sup> reported several cases of myocardial infarction and arterial thickening in children who consumed water containing about 0.6 mg/l arsenic.

Arsenic ingestion through food or water may have serious effects on the human cardiovascular system. Both acute and chronic arsenic exposure cause altered myocardial depolarization and cardiac arrhythmias that may lead to heart failure.<sup>36, 53</sup> Low level arsenic exposure by humans may also cause vascular system damage, a classical example of which is Blackfoot disease, which is endemic in an area of Taiwan where most drinking water contains 0.17 to 0.8 ppm arsenic<sup>126</sup>, corresponding to doses of about 0.01 to 0.5 mg As/kg/day.<sup>32</sup> In ground water arsenicosis of West Bengal this ischaemic gangrene from vasculitis are not seen probably due to less arsenic concentration circulating in blood stream.<sup>113</sup>

Effects of arsenic on the vascular system have also been reported in a number of other populations. In Chile, ingestion of 0.6 to 0.8 mg/l arsenic in drinking water (equivalent to 0.02 - 0.06 mg As/kg/day) increased the incidence of Raynaud's disease and of cyanosis of fingers and toes.<sup>13, 143</sup> Thickening of blood vessels and their occlusion were noticed due to arsenic in beer poisoning.<sup>90, 110</sup> In a case of acute voluntary massive arsenic intoxication, the muscles showed hypercontracted fibres, myofibrillar disruption, mitochondrial abnormalities and cytoplasmic vacuoles.<sup>37</sup> No data are available for cardiovascular effects due to organoarsenicals.

### **C. Gastrointestinal Effect:**

Gastrointestinal symptoms are common in acute poisoning but not in chronic like ground water arsenicosis. Workers exposed to high levels of arsenic dusts or fumes suffer from nausea, vomiting and diarrhoea.<sup>83</sup> Clinical signs of gastrointestinal irritation from acute arsenic poisoning include burning lips, painful swallowing, thirst, nausea and several abdominal colic.<sup>19,33,52</sup> These symptoms are usually not detectable at exposure levels below 0.01mgAs/kg/day<sup>131</sup> and they decline within a short time after exposure ceases. The efficiency of absorption of inorganic arsenicals from the gastrointestinal tract is related to their water-solubility. Chakraborty and Saha<sup>22</sup> reported three deaths in India due to chronic arsenic poisoning by drinking water from tubewells having mean arsenic content of 0.64mg/l. The most likely mechanism of gastrointestinal toxicity is damage to the epithelial cells, with resulting irritation. Tay and Seal<sup>122</sup> noted gastrointestinal involvement in 17 of 74 people ingesting arsenic at an estimated dose of 3 to 10 mg/day through an herbal preparation.

#### **D. Hematological Effects:**

The haematopoietic system is also affected by both short- and long-term arsenic exposures. Anemia and leukopenia are common effects of poisoning and have been reported as resulting from acute<sup>3</sup> intermediate,<sup>43</sup> and chronic oral exposures.<sup>50</sup> These effects may be due to a direct haemolytic or cytotoxic effect on the blood cells<sup>72</sup> and a suppression of erythropoiesis.<sup>67</sup> No such effects were noticed in humans exposed chronically to 0.07 mg As/kg/day or less. Relatively high doses of arsenic have been reported to cause bone marrow depression in humans.<sup>33</sup> Mizuta et al.,<sup>81</sup> reported anemia and leukopenia in adults ingesting 3 mg As/day in soy sauce. The malnutrition is a major cause of anaemia in underdeveloped countries like India and Bangladesh. Hence the anaemia in patients of arsenicosis is to be properly judged for the amount of the two causes.

High concentration of arsine (10 ppm) cause death within hours<sup>2</sup> due to red blood cell haemolysis.<sup>117</sup> Low levels of arsenic (0.5-5.0 ppm) bring about these effects in a few weeks, and an average concentration of 0.5 mg/l (0.2mg/m<sup>3</sup>) is considered acceptable in the work place.<sup>2</sup> Renal damage is secondary and occurs due to clogging of nephrons with hemolytic debris.<sup>117</sup> Mono-, di-, and trimethylarsines are strong irritants but are less hemolytic than arsine.<sup>89</sup> Arsine exposure by humans is usually fatal without proper therapy.<sup>42</sup> Arsine breaks down in the body to inorganic arsenic and methylated derivatives (less toxic than arsine).

The mechanism of hemolysis involved depletion of intracellular GSH, resulting in oxidation of sulfhydryl groups in the hemoglobin from ferrous to ferric in mice and rats. Haemocyanin combines with

arsenic, which reduced oxygen uptake by cells and therapy prevents hatching.

### **E. Hepatic Effect:**

Arsenic was the first chemical agent to which liver disease was attributed in humans. Since the liver tends to accumulate arsenic with repeated exposures, hepatic involvement has been reported most commonly as a complication of chronic exposures over periods of months or years.<sup>8, 24</sup> Patients may first come to medical attention with bleeding esophageal varices, ascites, jaundice, or simply an enlarged tender liver. Hepatic lesion that formed after prolonged ingestion of arsenic-containing medicines (Fowler's Solution) have been described. Clinical examination often reveals that the liver is swollen and tender.<sup>22,78</sup> The analysis of blood sometimes shown elevated levels of hepatic enzymes.<sup>43</sup> These effects are most often observed after chronic exposures to as little as 0.02 to 0.1 mg As/kg/day.<sup>78,116</sup> Arsenic has been observed to produce mitochondrial damage and impaired mitochondrial functions, and accordingly might be expected to affect porphyrin metabolism. Franklin et al.,<sup>44</sup> Hepatic fatty infiltration and cirrhosis of the liver in patients who used Fowler's solution. Non cirrhotic portal fibrosis and finally cirrhosis with hepatic failure results in ascitis jaundice and coma.

### **F. Renal Effects:**

Like the liver, the kidneys will accumulate arsenic in the presence of repeated exposures. The kidneys are the major route of arsenic excretion, as well as major site of conversion of pentavalent arsenic into the more toxic and less soluble trivalent arsenic. Sites of arsenic damage in the kidney include capillaries, tubules, and glomeruli.<sup>115,119,137</sup>

Damaged proximal tubular cells lead to proteinuria and casts in the urine. Mitochondrial damage is also prominent in tubular cells. Oliguria is a common manifestation, but if acute arsenic poisoning is sufficiently severe to produce shock and dehydration, there is real risk of renal failure, although dialysis has been effective in overcoming this complication.<sup>49</sup>

Arsine-induced hemolysis is likely cause tubular necrosis with partial or complete renal failure, requiring hemodialysis for removal of the hemoglobin bound arsenic.<sup>42</sup>

#### **G. Dermal Effects:**

Skin disorders have been documented in several epidemiological studies in which people consumed drinking water that contained arsenic of levels of 0.01 to 0.1 mg As/kg/day or more. Characteristic effects of arsenic ingestion included generalized hyperkeratosis, warts or corns on the palms and soles, and areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back.<sup>12, 13, 21, 59,</sup>

61, 143, 107

Several epidemiological studies involving 20 to 200 people detected no dermal or other effects as a result of exposure to chronic doses of 0.003 to 0.01 mg As/kg/day.<sup>118, 131</sup> A chronic oral dose of 0.01 mg As/kg/day or less would pose little risk of noncancer effects in humans.

#### **H. Neurological Effects:**

Several studies have indicated that ingestion of inorganic arsenic can result in neural injury. Like the

cardiovascular system, both the peripheral and central components of the nervous system can be damaged by arsenic.<sup>103, 115, 136, 137</sup> In the experience of one of us KCS<sup>113</sup>, no neuropathy were found but one case of myopathy was seen. In acute high exposures (1 mg As/kg/day or more) often cause encephalopathy with such symptoms as headache, lethargy, mental confusion hallucination, seizures, and coma.<sup>25</sup> Individuals with repeated arsenic exposures frequently contract sensorimotor polyneuropathy, which usually, but not always, displays symmetrical involvement and which may resemble Landry-Guillain-Barre Syndrome in its presentation. Neuropathy may appear in 1 to 5 weeks after an acute exposure and is produced mainly by axonal degeneration.

Symptoms of chronic encephalopathy include persistent headache, diminished recent memory, distractibility, abnormal irritability, restless sleep, loss of libido, increased urinary urgency, and increased effects of small amount of ethanol.<sup>83</sup> Secondary depression, anxiety, panic attacks and somatizations are common, in addition to the organic cognitive impairment documented by neuropsychological testing.

Electromyographic technique (EMG) used to detect neuropathy showed decreased nerve condition amplitude with little change in nerve condition velocity.<sup>29</sup> Bansal et al.<sup>6</sup> reported asymmetric bilateral phrenic nerve involvement in a patient who was poisoned by arsenic.

Inhalation of inorganic arsenic can cause neurological injury in humans they may include peripheral neuropathy of both sensory and motor neurons causing numbness loss of reflexes, and muscle weakness.<sup>35</sup>

## **I. Developmental Effects**

It is not well established whether ingestion of inorganic arsenic can cause developmental abnormalities in humans. No overall association between arsenic in drinking water and congenital heart defects was found in a case-control study in Boston<sup>144</sup>, although an association with coarctation of the aorta was noted. Nordstrom et al.,<sup>96, 98</sup> found that babies born to women exposed to arsenic dusts during pregnancy had a higher than expected incidence of congenital malformations. The average birth weight of the babies was slightly below average.<sup>97</sup> The incidence of spontaneous abortion in women who lived near a copper smelter in Sweden tended to decrease as a function of distance.<sup>96</sup> A couple of studies reported an increased number of miscarriages among women who worked in the semiconductor industry, which cause arsine.<sup>18, 68</sup> No reports exist concerning the development effects of organoarsenical compounds in humans. In chronic arsenicosis from ground water, no development defect has been experienced by one of us (KCS).

## **J. Reproductive Effects**

Hardly any published information exists regarding reproductive effects in humans and animals after inhalation exposure to arsenic or organoarsenicals. The same is true for human oral exposure to these compounds.

## **K. Genotoxicity Effects**

Inhalation exposure to arsenic trioxide increased the frequency of chromosomal aberrations in the

peripheral lymphocytes of smelter workers<sup>8, 95</sup> and in fatal mouse livers of mothers exposed to 22 mg As/m<sup>3</sup> during the gestation period (days 9-12).<sup>85</sup> These data do not indicate that arsenic is mutagenic, but they do indicate that it is clastogenic. There is no conclusive evidence that arsenic causes point mutations in any cellular system.<sup>9, 27</sup> However, Li and Rossman<sup>74</sup> have shown that arsenite causes inhibition of DNA repair after the incision step in Chinese hamster V79 cells.

#### **L. Mutagenic Effects:**

Mutagenesis includes the induction of DNA damage and a wide variety of genetic alterations, which can range from simple gene mutations (DNA base-pair changed to grossly visible changes in chromosome structure or number clastogenesis). Some of these changes may cause genetic damage transmissible to subsequent generations, and/or some may cause cancer or their problems in the exposed generation.<sup>60</sup>

Arsenic has long been known to cause chromosomal damage, but most investigators have been unable to induce direct gene mutation.<sup>56,119</sup> This apparent paradox, plus occasional poor correlation between arsenic exposure dose and resultant frequency of chromosomal aberrations, have been explained by the concept that arsenic promotes genetic damage in large part by inhibiting DNA repair.<sup>10, 71, 95, 110</sup> The repair inhibition may be a basic mechanism for the comutagenicity and presumably the cocarcinogenicity of arsenic.<sup>100</sup>

Comparisons of chromosome aberration frequencies induced by trivalent and pentavalent arsenic have indicated that the trivalent forms are far more potent and genotoxic than the pentavalent forms.<sup>7, 86, 93</sup>

Enzymes such as superoxide dismutase and catalase that scavenge for Oxygen free radicals seem to provide protection against arsenic induced DNA damage, indicating a possible basis for the genotoxic effect of arsenic.<sup>94</sup>

#### **M. Immunologic Effect:**

The effect on the immune system of inhalation exposure to arsenic is not well studied. No abnormalities were detected in the serum levels of immunoglobulins of workers exposed to arsenic in a coal-burning power plant.<sup>10</sup> The levels of arsenic were not measured in this study and they may have been too small to cause significant damage.

#### **N. Carcinogenic Effect:**

Introduction of cancer appears to be the most striking long-term effect of chronic exposure to inorganic arsenic. Epidemiological studies have demonstrated an evident causal relationship between environmental, Occupational, and medical exposure of man to inorganic arsenic and cancer of the skin and lungs.<sup>42,64,71,72,90,92,104</sup> Most animal experiments, however, were not able to demonstrate carcinogenicity, except for very few observations of increased incidence of leukaemia and lung cancer.<sup>39,121</sup>

There exists a clear association between pre-cancerous dermal keratosis, epidermoid Carcinoma of the skin and to some extent, lung cancer and exposure of humans to water-soluble inorganic arsenic through drinking water with high natural arsenic content or through contaminated beer and wine. Epidemiological studies in Argentina, Chile, Canada, and Taiwan Suggest correlations between drinking water that contains

arsenic and blackfoot disease, Bowens disease and skin cancer.<sup>39</sup>

### **O. Cancer of the Respiratory System:**

An excess of deaths due to respiratory cancer has been observed among workers exposed to inorganic arsenic in the production and use of pesticides (spray) gold mining, and in the smelting of nonferrous metals, especially copper.<sup>5, 28, 39, 46, 69,102</sup>

An increase of lung cancer with increasing duration of exposure to arsenic compounds but not with non-arsenic products. Cases of lung cancer have also been reported among workers engaged in the spraying of insecticides containing inorganic arsenic. Fishbein<sup>39</sup> states that the probability of death from lung cancer in persons with arsenical keratosis is 5 to 10 times higher than expected and IARC<sup>64</sup> has conducted that "there is sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans. Therapy with inorganic arsenicals has also been associated with the development of precancerous skin lesions, multiple epitheliomatosis and bronchial carcinoma.

### **P. Cancer of the Skin:**

Skin cancer has been associated with inorganic arsenic exposure.<sup>38,92,124</sup> Skin cancers are mostly monocentric but sometimes multicentric cases are also found.<sup>114</sup> Table 1 shows the increasing incidence of arsenicosis. Several types of neoplastic changes of the skin, including, Bowen's disease and basal cell carcinoma of arsenical origin are usually multiple and located on the trunk.<sup>38,140</sup>

Squamous cell carcinomas develop prima from the keratoses on the extremities. Multiple basal cell carcinoma has been related to arsenical therapy<sup>34</sup> as also an epitheloid angiosarcoma for right adrenal gland.<sup>75</sup> The exposure occurred most frequent via the oral route, either through contaminated drinking water or medication. Ingestion has usually taken place over several decades with daily doses of several mg of arsenic. In various types of skin cancer, the most common being multiple basal cell carcinomas.

### **Q. Biochemical Effects**

Arsenical compounds are known to inhibit a number of important enzymes in both animals and humans. Phenylarsine oxide (PAO) blocks glucose transport activity by inhibiting insulin activation of glucose uptake in rat soleus muscles<sup>134</sup> and in 3T3-L1 adipocytes<sup>45</sup>, in which vicinal thiol are implicated in signal transmission, These vicinal groups includen -SH, -SH/-OH and -SH/-CO<sub>2</sub>H, which take part in insulinstimulated sugar transport.<sup>30, 58</sup>

Arsenite is rapidly and extensively accumulated in the liver, where it inhibits NAD-linked oxidation of pyruvate or ? -ketoglutarate. This occurs by complexation of trivalent arsenic with vicinal thiols necessary for the oxidation of this substrate.<sup>119</sup>

## **VI. TRANSFORMATION OF ARSENIC IN THE BODY**

Arsenic is a normal component of the human body. Once ingested, soluble forms of arsenic are readily absorbed from the gastrointestinal tract. Absorption rate estimates range from 40 to 100% for humans. Arsenate, As(V) whether inorganic or organic, is better absorbed than As(III) arsenite because

arsenate is less reactive with membranes of the gastrointestinal tract. Arsenic in drinking water is mostly in the arsenate form, and complete absorption of arsenic from water may occur.

Once absorbed, arsenic is transported by the blood to different organs in the body, mainly in the form of MMA. Typical levels in the blood of people who are not exposed to a significant source of arsenic pollution range from 1 to 5  $\mu\text{g/l As}^{31}$ ; levels in soft tissue range from 0.01 to 0.1  $\mu\text{g As/gm}$ .<sup>31</sup> The highest levels may be found in nails and hair (0.1 to 1  $\mu\text{g As/g}$ ) where arsenic accumulates over time.

Metabolism of arsenic in humans involves two processes. After entering a cell, arsenate is reduced to arsenite. Arsenite is then methylated to form MMA and DMA; this process occurs primarily in the liver.<sup>80,123</sup> Trimethylarsine oxide, although expected to be formed during arsenic metabolism has not been identified in humans, and its significance in organic metabolism is still not known.

Inorganic As(V) and As(III) have different mechanisms of action. Arsenate (As(V)) behaves very much like phosphate consequently, it can substitute for phosphate in normal cell reactions, interfering with normal cell functions.<sup>1,90</sup> In contrast, arsenite [As(III)] has a high affinity for thiol (-SH) groups in proteins, causing inactivation of a variety of enzymes.<sup>1,90,124</sup> Because arsenate is reduced in the body to arsenite, arsenate in drinking water may have a biological effect identical to arsenite.

In contrast to inorganic arsenic, neither MMA nor DMA binds strongly to molecules in humans. Hence their relative acute toxicity is less than that of inorganic arsenic form.<sup>1</sup> In general, inorganic As(V) is

one tenth as toxic as inorganic As(III), and MMA and DMA are less toxic than inorganic As(V).<sup>31</sup> After ingestion, inorganic arsenic that is not immediately excreted or absorbed by tissues is progressively detoxified through the methylation process. However, the chronic effects of a MMA DMA are not known<sup>1</sup>, only a few studies have evaluated DMA.<sup>31</sup>

The form of arsenic significantly affects the rate at which arsenic is excreted from the body. Some of the inorganic arsenic is excreted primarily via urine as the parent form of the ingested arsenic. After methylation, it is also excreted as MMA and DMA. Humans rapidly excrete most blood arsenic, with 50 to 90% cleared in two to four days<sup>31,90</sup>. The remainder is cleared 10-100 times more slowly.<sup>90</sup>

The pharmacokinetics of arsenic in the human body are not well understood. Although several pharmacokinetic models have been developed, they apply to short-term exposure (two to four rats) and have several limitations that cause them to be inaccurate projections.<sup>14</sup> Further development and refinement of pharmacokinetic and pharmacodynamic models are important, however. They may provide insight into arsenic health effects at low levels of exposure and help to interpret epidemiological studies on As, most of which have used ecological study design.

## **VII. HOW ARSENIC AFFECT OR DESTROY THE BODY ENZYMATIC SYSTEM**

Arsenite compound is mainly absorbed to the human elementary canal and it is deposited hugely to the various cells in the body. As a result it affects the enzyme activity in the cell and finally the affected cells are dead slowly.

**1st step.**

Pyruvic acid (which is obtained from the glucose of inside the cell mitochondria) breaks with the help of a special type of enzyme. The pyruvate oxidase complex is necessary for oxidative decarboxylation of pyruvate produce to acetyl coenzyme A and carbon dioxide before it enters the tricarboxylic acid cycle. In this process energy is store for workable of cells.

The enzyme system comprises several enzymes and cofactors one protein molecule of enzyme having one lipoic acid. And in one lipoic acid having two sulfhydryl (-SH) or thiol group, which is essential for its workability.

In the presence of trivalent arsenic (Arsenite) it replace the two Hydrogen from the thiol group and attached with sulfur molecule and formed a dihydrolipoyl-arsenite chelate complex, which preveating the reoxidation of the dihydrolipoyl group necessary for continued enzymatic activity, and this pivotal enzyme step is block. As a result amount of pyruvate in blood increases energy production is reduced and finally the cell damage slowly.

In the same manner arsenic destroy workability of another enzyme and reduced production of succinyl coenzyme A and finally production of ATP reduced. If arsenic is deposited in long time then it breaks the ATP block the energy supply to the cells.

## Step 2

The arsenate form of inorganic arsenic are available in nature. This also block the enzymatic activity in mitochondria but in different way. The next steps of ADP from the continuing enzymatic activity combine with inorganic phosphate and produce ATP. This reaction is called oxidative phosphorylation. Since arsenic can replace phosphorus, so it combine with ADT to replacing phosphate and subsequent formation of an unstable arsenate ester bond that is rapidly hydrolysat. As a result though oxidation is occur but production of ATP through phosphorylation is hampered and source of energy in cell reducing continually not only this but also it disturb the electron transfer of inorganic phosphorus with ATP. Thus, the so-called high-energy bonds of adenosine triphosphate are not conserved in the presence of arsenate. This process is termed arsenolysis.<sup>130</sup> Arsenic may therefore be doubly toxic to cellular respiration by inhibiting energy-Linked functions of the mitochondria in two very different ways.

1. Trivalent arsenic inhibits the reduction of nicotinamide adeine dinucleotide by deactivating critical enzymes in the tricarboxylic acid cycle, and
2. Pentavalent arsenic uncouples oxidative phosphorylation by arsenolysis.

Another important enzymatic reaction is the production of ATP with succinic acid or succinate through flevo protein reduction, Arsenate compound disturbed in this reaction also, as a result energy supply in cells reduced.

## VIII. REMEDY FOR ARSENICOSIS

## **A. Acute Arsenic Poisoning**

Acute arsenic toxicity is practically not seen in the present days. Because there are many easier ways of suicidal and homicidal poisoning. Treatment is just like cholera and dehydration.

## **B. Chronic Arsenic Poisoning**

Arsenic has been used as a medicine and as a poison since humans first became interested in chemistry. The untoward effect of "medicinal" arsenic, primarily inorganic arsenite, have only recently been appreciated because their ill effects are of a chronic nature and large epidemiologic databases are needed to define deleterious outcomes. The toxic properties of all arsenic preparations are dose-dependent. Regarding the administration of arsenic, the dictum of paracelsus (1493? -1541) is appropriate to remember: "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy. "Arsenic is rapidly cleared from the blood stream and the major route of arsenic elimination is through the kidneys as methylated arsenic metabolites, the preferred sample for diagnostic analysis is a 24hrs urine collection, Arsenic exposure may also be assessed by analysing the content in hair and nails because arsenic tends to accumulate in these tissues over time. Analysis of scales has been form as additional measure by Prof. Saha.

In cases of chronic arsenic poisoning one should consider BAL (British antilewisite) as a chelator the signs of arsenicosis are severe or the patient is in complications.<sup>77</sup> Treatment by BAL is superior to penicillamine.

During the clinical phase, when symptoms like melanosis and keratosis appear on the skin, chelating

agents like BAL, Penicillamine, DMSA/DMPS help in clearing melanosis. Mechanical scraping of soles of feet can be done to relieve keratosis. Urea and salicylate ointments can also be used. Prolonged use of chelating agent BAL with mechanical scraping of water soaked keratotic soles and palms give encouraging results. Urea (20%) in cream or vaseline, followed by 6-10% salicylic acid, also helps for smoothening of skin. Follow-up of treated patients at monthly interval for clinical and chemical assessment is helpful for final assessment of the treatment<sup>113</sup>. During the phase of internal complications, symptomatic treatment has to be applied using antibiotics. Glucose-Methionine has to be applied for the treatment of liver damage leading to ascitis and portal hypertension.

In case of malignancy, chelating agents, become useless. Early surgical removal of the affected parts (if no melanosis or granular spread) and chemotherapy may prolong life. But such treatments cannot cure the disease after cancer sets in; they can only prolong the suffering using highly expensive drugs.

Dimercaprol (2, 3-dimercaptopropanol) is the traditional chelating agent used, but Penicillamine has been used with some success.<sup>105</sup> Parenteral dimercaprol is administered intramuscularly at an initial dose of 3 to 5 mg/kg of body weight every 4 hr. the dose should be tapered but administration continued until the urinary arsenic excretion is less than 50µg per 24 hr. This therapy is frequently effective in preventing or neutralizing systemic toxicity. In most cases, the degree of recovery from neuropathy, aplastic anaemia, encephalopathy and jaundice is limited and directly related to the initial severity of the systemic involvement and the rapidity with which chelation therapy is initiated.

Penicillamine, although only a monothiol agent, has been used successfully; its great advantage is that it may be orally administered. Both agents have a high frequency of side effects, although this is less of a problem in the presence of large amounts of body arsenic.

A recently reintroduced drug that appears to be a promising agent for treating arsenic poisoning is 2, 3-dimer captosuccinic acid. this is a dithiol agent that can be orally administered and has few reported side effect.<sup>57</sup> Table 2 shows the medicine for arsenicosis disease.

## **IX. PREVENTION OF ARSENIC POISONING IN HUMANS**

It is obvious that high-arsenic drinking water may be a factor in arsenic toxicosis in human beings. It seems to be important in the control of the disease to consider how to prevent arsenic intake from drinking water. The symptoms and signs of arsenic poisoning may be reduce if the quality of drinking water improved. In some cases, the symptoms and signs of arsenic poisoning were reduced three years after the quality of drinking water improved. The morbidity rate also declined.

Numerous studies suggested that improvement of water quality, the rate of improvement in the symptoms and signs of arsenic poisoning in human beings may increase with a decrease in arsenic level in the drinking water source.

Furthermore, it was observed that new cases of human poisoning occurred only when arsenic concentrations in the drinking water source exceeded 0.15 mg/L. (Table-3). At the same time, it was also

found that arsenic levels in the urinary samples from cases of human poisoning also declined with a decrease in the arsenic levels in water source for drinking. (Table-4). Thus, it may be essential for the control of the disease to improve water quality in areas of endemic arsenic toxicosis.<sup>134</sup>

## **X. CONCLUSIONS**

1. Exposure to arsenic may come from natural source, from industrial source, or from administered acute poisoning.
2. Chronic arsenical dermatosis arises from consuming arsenic contaminated drinking water for long time.
3. Ingestion via food or water is the main pathway of arsenic into the organism.
4. Humans are more sensitive to arsenic than animals.
5. Weak and malnourished people can be easily affected by arsenic contaminated water or fume or dust or contact at the skin.
6. Melanosis may disappear by using medicine but keratosis can not alter though further complication may be prevented.
7. No medicine was found effective once complication developed.
8. Arsenic free water or environment or decrease in arsenic concentration level is only the solution of arsenicosis.

**TABLE 1      Increasing incidence of arsenicosis-cumulative (1983-97)**

Year	A. D.	A. B.	A. V.	ASD	Cancer incidence				
					Skin	Lung	Blad.	GUTR	Total
1983	4	5	5	127	0	0	0	0	0
1984	5	12	15	241	1	0	0	0	1
1985	6	17	24	485	3	0	0	0	3
1986	6	30	40	1068	3	0	0	0	3
1987	6	40	61	1214	6	0	0	0	6
1988	6	42	78	2026	30	3	3	2	38
1990	6	44	123	24000	No data				
1993	6	47	415	83000					
1994	6	47	428	85600					
1995	6	54	544	108800	139	16	3	2	160
1996	7	60	638	200000	196	19	3	2	220

1997	9	74	966	200000	198	19	3	2	222
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A. D.- Affected Districts

A. B.- Affected Blocks

A. V.- Affected Village

Blad.- Bladder

GUTR- Genito Urinary Tract

**TABLE 2      Medicine for arsenic diseases, which are tried.**

<b>Chelating agent</b>	<b>Therapeutic use</b>
Dithiol & monothiol agents (BAL) Penicillamine SMSA & DMPS	A Specific line of treatment for relief of clinical manifestations and chelating reduction of arsenic stores in the body, reducing subsequent-cancer risk.
DMSA &DMPS	Effective in the treatment of chronic arsenic toxicity, but costly and not in available in India.
BAL (British Antilewisite)	Used as a chelator when arsenic extraction from tissue is required, treatment for severe arsenic poisoning.
Dimercaprol (2, 3-dimercaptopropanol)	Traditional chelating agent
Penicillamine (monothiol agent)	This is also a chelating agent, which is used successfully with its great advantage that it may be orally administered.
2,3-dimercapto succinic acid (Dithiol agent)	Recently reintroduced drug that appears to be promising agent for treating arsenic poisoning.

Results as per experience of one of us (KCS) are not satisfactory. Melanosis disappears or diminished in 1-2 month appreciately but keratosis is not altered. It prevents the further complications but malignancy may not be prevented.

**TABLE 3 Relationship Between the Rate of Improvement in Symptoms and Signs and Arsenic Level in Drinking Water.**

Water arsenic (mg/L)	Improvement in symptoms and signs.			New class		
	Number of Cases	Number improved		Number observed	New class	
		Cases	Rate (%)		Cases	Rate (%)
0.0 – 0.04	13	10	76.9	26	0	0
0.05 - 0.14	19	11	57.9	43	0	0
0.15 - 0.25	61	35	57.4	47	3	6.4
0.26 - 0.4	81	21	25.9	254	25	16.2

0.50 and up	7	0	0	4	3	-
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**TABLE 4 Correlation Between Arsenic Level in New Water Source and Arsenic Level in Urine.**

Water arsenic level (mg/l)	Cases observed	Urine Arsenic level (mg/l)	
		Mean	SE
0.0 - 0.04	32	0.03	0.005
0.05 - 0.14	9	0.059	0.013
0.15 - 0.25	10	0.127	0.024
0.26 - 0.3	7	0.152	0.014

0.40 and up	14	0.228	0.037
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Photograph 1. Melanosis (Whole body)

Photograph 2. Spotted melanosis (rain drop disease)  
Village: Jampukur, Kaligang, Dist. Nadia

Photograph 3. Leucomelanosis, Village: Bishnupur, Gaighata  
Block, Dist. North 24 Pargana.

Photograph 4. Spotted and diffuse with nodular keratosis on sole.  
Vill. Chandpur Rail line, Bashir Hat, Block-II, Dist. North 24-Pargana.

Photograph 5. Palpable nodules in dorsum on hands, feet and legs,  
Village: Mandra, Purbasthli Block I, Dist: Burdwan.

Photograph 6. Squamous cell carcinoma (SCC), Asokenagar,  
Habra Block II, District : North 24-Parganas.