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 nonspecific symptoms may also be present in many other diseases. Medicine used for the remedy of arsenicosis has been found to be unsatisfactory by repeated application and experience. Melanosis may disappear but keratosis is not altered, although it can prevent further complication. Once the 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 was improved. Arsenic-free water or a decrease in the 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.[62] 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.[99] In the experience of one of us (KCS), food grown in arsenic-affected areas arsenic is not found inside foodlike cereals, pulses, or fruits, but may be found in the external layer of food or fruits

due to spread of arsenicated water. Similarly, milk of arsenic-affected cows is free from arsenic due to modification inside the 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 a highly emotionally 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.[20]

Arsenic is a protoplastic poison due to its effect on a sulfydryl group of cells interfering with cells enzymes, cell respiration, and mitosis.[55] Chronic arsenical poisoning and medicinal use of arsenic are well known. Arsenic was used orally as Fowler's solution in tonic mixtures and in the treatment of asthma, leukemia, and other malignancies.[73,141] Parenterally, arsenic was used in the past for the treatment of syphillis,[82] topical eosinophilia,[76] trepanosomiasis,[84,88] Lichen planus, verruca planum, and psoriasis.[54] Domestic, agricultural, and industrial uses of arsenic[23] in the form of insecticides, weedicides, rodenticides, and arsine are becoming rarer because of the advent of low-toxic pesticides. Chronic hepatitis and hepatic cirrhosis have been described due to consuming arsenic-contaminated beer.[108,138] Nondermatological features of chronic arsenical poisoning by consuming arsenic-contaminated drinking water were first reported in 1961 by Tseng et al. in Taiwan,[126] followed by Rosenberg[109] in Chile and by Datta in India.[26] Saha's report[112] is the first report in the 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.[64] This obviously also applies to compounds whose toxicity greatly varies. The inorganic forms of arsenic exhibit the highest toxicity level,[40] 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.[41,101] 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 allows 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 Organization (WHO), the provisional total daily intake should not exceed

2 μg 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, that is, accidental source. Self-administration of arsenic, unintentionally, that is, accidental consumption by children or deliberate (i.e., homicidal or suicidal in attempts by adults) represents the rare causes of acute poisoning.[47] 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 the overwithdrawal 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 colorless, odorless, 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.[42]

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, because it is more lipid-soluble than the pentavalent form.[137] 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.[132] 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 inhalated arsenic is well absorbed through the gastrointestinal tract and lung into the bloodstream. Ninety-five 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.[63] After absorption through lungs and the gastrointestinal 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 is excreted mainly through the urine. Most arsenic absorbed into the body is converted by the liver to a less toxic methylated form that is efficiently excreted in the urine. The rate of decrease of arsenic in the skin appears to be especially low compared with the rate for other organs.[129,139]

III. ARSENIC POISONING

A. Acute Poisoning

Symptoms of acute intoxication usually occur within 30 min 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 flusking skin. Severe nausea and vomiting, colicky abdominal pain, and profuse diarrhea with rice-water stools abruptly ensue. Capillary damage leads to generalized vasodilation, transudation of plasma, and vasagenice 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 h from irreversible circulatory insufficiency, it may result from hepatic or renal failure over the next several days. Cardiac manifestations include acute cardiomyopathy, subendocardial hemorrhages, and electrocardiographic changes. The most common changes on an electrocardiogram are prolonged QT intervals and nonspecific ST-segment changes.[50]

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[113, 114] by Prof. K. C. Saha in July 1982 at School of Tropical Medicine, Calcutta.[112, 113]

The cutaneous changes are characteristic yet nonspecific. 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.[103] 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.[113, 114] 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,[79] and one may speculate that arsenic causes 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.[120] Brittle nail, patchy alopecia, and facial edema are reported in the literature in arsenical skin diseases. One of us (KCS)[113] experienced nonpitting edema of the feet and rarely conjunctival congestion as additional signs in arsenical dermatosis (ASD).

Anemia and leukopenia are almost universal with chronic arsenic exposure. Thrombocytopenia also frequently occurs. The anemia is usually normochromic and normocytic and caused at least partially by hemolysis.[67] Interference with folate metabolism and DNA synthesis may result in megaloblastic changes.[135] In underdeveloped countries such as India and Bangladesh, the presence of anemia, leukopenia, and thrombo cytopenia from arsenic are to be carefully assessed, keeping in mind the common association of anemia and leukopenia from malnutrition.

IV. PRIMARY SYMPTOMS AND DIAGNOSIS OF ARSENIC DISEASES

A. 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 largely depends on the awareness of the problem. Among the people who were taking high-arsenic water, early symptoms included, following nonspecific symptoms, which can be present in many other diseases.

- Palpitations
- Fatigue

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

B. Stages of Clinical Features of Arsenic Toxicity

Arsenical toxicity or arsenicosis develops insidiously after 6 months to 2 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,[114] which are now known as Saha's classification of stages. These are (1) preclinical, (2) clinical, (3) internal complication, and (4) malignancy.

1. Preclinical (Asymptomatic) Stage

This may be subdivided into labile, chemical, or blood phase (transient). Urine showing arsenic metabolites, Dimethylarsonic acid (DMAA), and Trimethl arsinic acid (TMAA) during the intake of groundwater containing high arsenic concentration; stable, subclinical, 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).

a. Tissue Phase (Stable)

In this phase, examination of nails, hair, and skin scales or other body tissues reveals high arsenic concentration, although 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. The idea of skin scales for arsenic was also first observed by Prof. Saha.[113]

a. Onset

The features of arsenical toxicity appear gradually and slowly with time. Six months to 10 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 signs are often mild. On the other hand, if these conditions are not satisfied, the symptoms may develop between 6 months to 2 years.

b. Major Dermatological Signs

i. Melano-Keratosis

Melanosis, that is, dark pigmentation-diffuse and/or spotted keratosis, that is, dry, rough-spotted nodules in the palms and/or the 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 such as arsenicosis appear in later life.

ii. Melanosis

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

iii. Spotted or Rain Drop Pigmentation (Spotted Melanosis)

This is usually seen on chest, back, or limbs. This is a fairly common symptom. (Figure 2 shows a patient with severe spotted melanosis.) Fifty percent of the patients show spotted melanosis in chest, back, and sometimes in the limbs (i.e., hands and legs).

iv. Spotted and Diffuse Keratosis

When on the palms and soles (Figure 3), they are signs of moderate to severe toxicity. Rough, dry, spotted nodules (spotted keratosis) appear after 5 to 10 years in the palms and feet. Still later (>10 years), the skin becomes dry and thickened. This stage is called diffuse keratosis. Gradual thickening of the soles can give rise to cracks and fissures (hyperkeratosis).

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

FIGURE 1. Melanosis (whole body).

FIGURE 3. Spotted and diffuse with nodular keratosis on sole.
Vill. Chandpur Rail line, Bashir Hat, Block-II, Dist. North 24-Pargana.

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. Stimulation of melanocytes probably produces the pigmentation, and damage in the later stage is responsible for the depigmentation spots. Leucomelanosis is common (white and black in color) in persons with advanced arsenicosis or who have stopped drinking arsenic-contaminated water but had spotted melanosis earlier. (Figure 4 shows such a case in the Nadia district.)

vi. Dorsal Keratosis

This is rough dry skin often with palpable nodules (spotted keratosis) on dorsum of hands, feet, and legs and are the signs seen in a severe case (Figure 5). If the

FIGURE 4. Leucomelanosis, Village: Bishnupur, Gaighata
Block, Dist. North 24 Pargana.

arsenic intake is high or the disease is of long duration — more than 10 to 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 Palmoplanter Keratosis)

This combination in post-childhood age almost always points to arsenic toxicity, excluding other causes of isolated pigmentation and keratosis (nodular rough skin), and Palmoplanter skin was involved in early phase and keratosis of the limbs in the later phase.

FIGURE 5. Squamous cell carcinoma (SCC), Asokenagar. Habra Block II, District : North 24-Parganas.

C. 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 Edema

In rare cases edema appears in the feet. which does not pit on pressure without any history of attracts of pain or fever, differentiationship from filarial lymphedema. This was also first pointed out as an additional sign of arsenicosis by one of us (KCS).[113]

iii. Conjunctival Congestion

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

3. Stage of Internal Complications

In this stage, nondermatological toxic features appear in addition to the 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 such as lungs, liver, muscles, eyes, and vessels are affected. Clinical symptoms are associated with biochemical evidence of organ dysfunction as well as histological, histochemical abnormalities, and high concentrations of arsenic in the different organs involved. Liver enlargement (hepatomegaly), spleen enlargement (splenomegaly), and fluid in abdomen ascites are seen in several cases.

4. Stage of Malignancy

Malignancy affecting skin, lungs, bladder uterus, or other organs develops if the patient survives the stage of complications. Malignancy does not develop before 10 years of arsenic exposure.[113] Usually after 15 to 20 years from the onset of first symptoms, cancer develops. Skin cancers are mostly monocentric, but sometimes multicentric cases are also found. They usually have slow progress for years. However, sometimes in 6 months malignancy extends to neighboring glands and in 9 months to 1 year the patient often expires.

1. Skin, lungs, bladder, genito urinary tract, etc.
2. Squamous cell carcinoma (Figure 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 to 20 years.

5. Other Rare Signs

1. Arterial insufficiency (Blackfoot disease of Taiwan).
2. 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 to 0.1 mg/kg/d) causes neurological and hematological 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/d.[17]

FIGURE 6. Palpable nodules in dorsum of hands, feet, and legs. Village: Mandra, Purbasthali Block-I, Dist: Burdwan.

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.[87]

A. Respiratory Effects

Effects of arsenic on the human respiratory system have been reported from both 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.[27] Very high exposure to unprotected workers may manifest perforated nasal septum after 1 to 3 weeks of exposure,[106] but such effects are minor or absent at exposure levels of 0.01 to 1 mg/m^3.[65] A fatal case of arsenic trioxide inhalation manifested widespread tracheobronchial mucosal and sub-mucosal hemorrhages with mucosal sloughing, alveolar hemorrhages, and pulmonary edema.[48] Chronic asthmatic bronchitis and asthma is a common complication of

groundwater arsenic toxicity.[113] 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.[4,70,133] Long-term inhalation of inorganic arsenic could injure the blood vessels or the heart. Zaldivar[143] 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.[36,53] Low-level arsenic exposure by humans may also cause vascular system damage, a classic 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,[126] corresponding to doses of about 0.01 to 0.5 mg As/kg/d.[32] In groundwater arsenicosis of West Bengal, this ischenice gangrene from vasenlitis is not seen, probably due to less arsenic concentration circulating in the bloodstream.[113]

The 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 to 0.06 mg As/kg/d) increased the incidence of Raynaud's disease and of cyanosis of the fingers and the toes.[13,143] Thickening of blood vessels and their oclution were noticed due to arsenic in beer poisoning.[90,110] In a case of acute voluntary massive arsenic in toxicaction, the muscles showed hypercontracted fibers, myofibrillar disruption, mitochondrial abnormalities, and cytoplasmic vacuoles.[37] No data are available for cardiovascular effects due to organoarsenicals.

C. Gastrointestinal Effect

Gastrointestinal symptoms are common in acute poisoning but not in chronic poisoning like ground-water arsenicosis. Workers exposed to high levels of arsenic dusts or fumes suffer from nausea, vomiting, and diarrhea.[83] Clinical signs of gastrointestinal irritation from acute arsenic poisoning include burning lips, painful swallowing, thirst, nausea, and several abdominal colic.[19,33,52] These symptoms are usually not detectable at exposure levels below 0.01 mgAs/kg/d[131] and they decline within a short time after the exposure ceases. The efficiency of absorption or inorganic arsenicals from the gastrointestinal tract is related to their water solubility. Chakraborty and Saha[22] reported three deaths in India due to chronic arsenic poisoning by drinking water from tubewells having mean arsenic content of 0.64 mg/l. The most likely mechanism of gastrointestinal toxicity is damage to the

epithelial cells, with resulting irritation. Tay and Seal[122] noted gastrointestinal involvement in 17 of 74 people ingesting arsenic at an estimated dose of 3 to 10 mg/d through an herbal preparation.

D. Hematological Effects

The hematopoietic 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,[3] intermediate,[43] and chronic oral exposures.[50] These effects may be due to a direct hemolytic or cytotoxic effect on the blood cells[72] and a suppression of erythropoies.[67] No such effects were noticed in humans exposed chronically to 0.07 mg As/kg/d or less. Relatively high doses of arsenic have been reported to cause bone marrow depression in humans.[33] Mizuta et al.[81] reported anemia and leukopenia in adults ingesting 3 mg As/d in soy sauce. Malnutrition is a major cause of anemia in underdeveloped countries such as India and Bangladesh. Hence, the anemia in patients of arsenicosis is to be judged properly for the weight of the two causes.

High concentrations of arsine (10 ppm) cause death within hours[2] due to red blood cell hemolysis.[117] Low levels of arsenic (0.5 to 5.0 ppm) bring about these effects in a few weeks, and an average concentration of 0.5 mg/l (0.2 mg/m^3) is considered acceptable in the workplace.[2] Renal damage is secondary and occurs due to clogging of nephrons with hemolytic debris.[117] Mono-, di-, and trimethylarsines are strong irritants but are less hemolytic than arsine.[89] Arsine exposure by humans is usually fatal without proper therapy.[42] 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. Hemocyanin combines with arsenic, which reduces 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. Because 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.[8,24] Patients may first come to medical attention with bleeding esophageal varices, ascites, jaundice, or simply an enlarged tender liver. Hepatic lesions 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.[22,78] The analysis of blood sometimes shown elevated levels of hepatic enzymes.[43] These effects are most often observed after chronic exposures to as little as 0.02 to 0.1 mg As/kg/d.[78,116]

Arsenic has been observed to produce mitochondrial damage and impaired mitochondrial functions, and accordingly might be expected to affect porphyrin metabolism. Franklin et al.[44] found hepatic fatty infiltration and cirrhosis of the liver in patients who used Fowler's Solution. Noncirrhotic portal fibrosis and finally cirrhosis with hepatic failure result in ascitis jaundice and coma.

F. Renal Effects

Like the liver, the kidneys 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.[115,119,137]

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 a real risk of renal failure, although dialysis has been effective in overcoming this complication.[49]

Arsine-induced hemolysis is likely to cause tubular necrosis with partial or complete renal failure, requiring hemodialysis for removal of the hemoglobin-bound arsenic.[42]

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/d or more. Characteristic effects of arsenic ingestion included generalized hyperkeratosis, warts, or corns on the palms and the soles, and areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back.[12,13,21,59,61,143,107]

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/d.[118,131] A chronic oral dose of 0.01 mg As/kg/d or less would pose little risk of non-cancer 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.[103, 115, 136, 137] In the experience of one of us (KCS).[113] no neuropathy was found, but one case of myopathy

was seen. In acute high exposures (1 mg As/kg/d or more) often cause encephalopathy with such symptoms as headache, lethargy, mental confusion/hallucination, seizures, and coma.[25] Individuals with repeated arsenic exposures frequently contract sensorimotor polyneuropathy, which usually, but not always, displays symmetrical involvement and 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.[83] 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.[29] Bansal et al.[6] 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.[35, 83]

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,[144] although an association with coarctation of the arota was noted. Nordstrom et al.[96,98] found that babies born to women exposed to arsenic dusts during pregnancy had a higher than expected incidence of congenial malformations. The average birth weight of the babies was slightly below average.[97] The incidence of spontaneous abortion in women who lived near a copper smelter in Sweden tended to decrease as a function of distance.[96] A couple of studies reported an increased number of miscarriages among women who worked in the semiconductor industry, which cause arsine.[18,68] No reports exist concerning the development effects of organoarsenical compounds in humans. In chronic arsenicosis from groundwater, 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 perpheral lymphocytes of smelter workers[8,95] and in fatal mouse livers of mothers exposed to 22 mg As/m^3 during the gestation period (days 9 to 12).[85] 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.[9,27] However, Li and Rossman[74] 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.[60]

Arsenic has long been known to cause chromosomal damage, but most investigators have been unable to induce direct gene mutation.[56,119] This apparent pardon, 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.[10,71,95,110] The repair inhibition may be a basic mechanism for the comutagenicity and presumably the cocarcinogenicity of arsenic.[100]

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.[7,86,93] Enzymes such as superoxide disumutese 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.[94]

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 pone plant.[10] The levels of arsenic were not measured in this study and they may have been too small to cause significant damage.

N. Carcinogenic Effect

The introduction of cancer appears to be the most striking long-term effect of chronic expose 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.[42,64,71,72,90,92,104] Most animal experiments, however, were not able to demonstrate concinogenicity, except for very few observations of increased incidence of leukemia and lung cancer.[39,121]

There exists a clear association between precancerous 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 a 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.[39]

O. Cancer of the Respiratory System

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

An increase in lung cancer is associated with an 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[39] states that the probability of death from lung cancer in persons with arsenical keratosis is 5 to 10 times higher than expected, and the IARC[64] has concluded 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.[38,92,124] Skin cancers are mostly monocentric but sometimes multicentric cases are also found.[114] 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.[38,140]

TABLE 1
Increasing the Incidence of Arsenicosis Cumulative (1983-1997)

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					
1993	6	47	415	83000			No data		
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

Note: A. D., affected districts; A. B., affected blocks; A. V., affected village; Blad., bladder; GUTR, genito urinary tract.

Squamous cell carcinomas develop prima from the keratoses on the extremities. Multiple basal cell carcinoma has been related to arsenical therapy[34] and also an epitheloid angiosarcoma for right adrenal gland.[75] 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 milligrams 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[134] and in 3T3-L1 adipocytes,[45] in which vicinal thiol are implicated in signal transmission. These vicinal groups include $-SH$, $-SH/-OH$, and $-SH/-CO_2H$, which take part in insulinstimulated sugar transport.[30,58]

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

V. 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 μg/l As;[31] levels in soft tissue range from 0.01 to 0.1 μg As/g.[31] The highest levels may be found in nails and hair (0.1 to 1 μg 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.[80,123] 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, interesting with normal cell functions.[1,90] In contrast, arsenite [As(III)] has a high affinity for thiol (-SH) groups in proteins, causing inactivation of a variety of enzymes.[1,90,124] 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.[1] 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).[31] 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,[1] only a few studies have evaluated DMA.[31]

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 2 to 4 d.[31,90] The remainder is cleared 10 to 100 times more slowly.[90]

The pharmacokinetics of arsenic in the human body are not well understood. Although several pharmacokinetic models have been developed, they only thinly apply to short-term exposure (two to four rats) and have several limitations that cause them to have inaccurate projection.[14] 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.

VI. HOW ARSENIC AFFECTS OR DESTROYS THE BODY ENZYMATIC SYSTEM

Arsenite compound is mainly absorbed to the human elementary canal and 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 die slowly.

A. Step 1

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

The enzyme system comprises several enzymes and cofactors, one protein molecule of enzyme having one lipoic acid. In one lipoic acid there are two sulfhydryl (–SH) or thiol groups, which is essential for its workability.

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

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

B. Step 2

The arsenate form of inorganic arsenic is available in nature. This also blocks the enzymatic activity in mitochondria, but in a different way. The next steps of ADP from the continuing enzymatic activity combined with inorganic phosphate

produce ATP. This reaction is called oxidative phosphorylation. Because arsenic can replace phosphorus, it combines with ADT to replace phosphate and the subsequent formation of an unstable arsenate easter bond that is rapidly hydrolysated. As a result though oxidation occurs, but production of ATP through phosphorylation is hampered and the source of energy in cells, reducing not only this but also disturbing 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.[130] Arsenic therefore may 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 tricarbonylic acid cycle
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 in this reaction is also disturbed; as a result, energy supply in the cells are reduced.

VII. REMEDY FOR ARSENICOSIS

A. Acute Arsenic Poisoning

Acute arsenic toxicity is practically not seen presently, because there are many easier ways of suicidal and homicidal poisoning. Treatment is just like that for 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 been appreciated recently because their ill effects are of a chronic nature, and large epidemiologic databases are needed to define the 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 bloodstream and the major route of arsenic elimination is

through the kidneys as methylated arsenic metabolites. The preferred sample for diagnoestic analysis is a 24-h urine collection. Arsine exposure may also be assessed by analyzing the content in hair and nails because arsenic tends to accumulate in these tissues over time. Analysis of scales has been formed as an additional measure by Prof. Saha.

In cases of chronic arsenic poisoning one should consider BAL (British antilewisite) as a chelator if the signs of arsenicosis are severe or if the patient has complications.[77] Treatment by BAL is superior to penicillamine.

During the clinical phase, when symptoms like melanosis and keratosis appear on the skin, cheleting agents like BAL, Penicillamine, and DMSA/DMPS help in clearing melanosis. Mechanical scraping of the soles of the feet can be done to relieve keratosis. Urea and salicylate ointments can also be used. Prolonged used of the chelating agent BAL with mechanical scraping of water-soaked keratotic soles and palms gave encouraging results. Urea (20%) in cream or vaseline, followed by 6 to 10% salicylic acid also helps for smoothening of the skin. Follow-up of treated patients at monthly intervals for clinical and chemical assessment is helpful for the final assessment of the treatment.[113] During the internal complications phase, symptomatic treatment has to be applied using antibiotics. Glucose-

TABLE 2
Medicine for Arsenic Diseases, Which are Tried

Chelating agent	Therapeutic use
Dithiol and monothiol agents (BAL) Penicillamine SMSA and 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 and 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 that 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

Note: Results as per experience of one of us (KCS) are not satisfactory. Melanosis disappears or diminished in 1 to 2 months appreciatively, but keratosis is not altered. It prevents the further complications, but malignancy may not be prevented.

Methionine has to be applied for the treatment of liver damage leading to ascitis and portal hypertension.

In the case of malignacy, chelating agents become useless. Early surgical removal of the affected parts (if no melanosis or granular spread) and chemotherapy may prolong life. However, 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.[105] Parenteral dimercaprol is administered intramuscularly at an initial dose of 3 to 5 mg/kg of body weight every 4 h. The dose should be tapered, but administration continued until the urinary arsenic excretion is less than 50 kg per 24 h. This therapy is frequently effective in preventing or neutralizing systemic toxicity. In most cases, the degree of recovery from neuropathy, aplastic anemia, encephalopathy, and jaundice is limited and directly related to the initial severity of the systemic involvement and the rapidity with which chelation therapy in 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 effects.[57] Table 2 shows the medicine for arsenicosis disease.

VIII. 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 3 years after the quality of the drinking water is 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.[134]

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 Improved			New class	
	Number of cases	Cases	Rate (%)	Number observed	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	—

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

IX. 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 malnutritious people can easily be affected by arsenic-contaminated water or fume or dust or contact at the skin.
6. Melanosis may disappear by using medicine, but keratosis cannot alter, although further complications 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 for arsenicosis.

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