Arsenicosis: Review of Recent Advances

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Abstract

Human health in the past and presently is influenced by the amounts and proportion of chemical elements to which humans have been exposed. Arsenic, as a therapeutic agent was known to ancient Greeks and Romans. Ehrlick introduced organic arsenicals as anti linetic agents but with advent of penicillin these have nearly become obsolete. Once considered toxic, harmful to humans, arsenic is now considered an essential ultra trace element at least in animals. Now the impact of arsenic on health is more from industrial and environmental than medicinal exposure.

This article reviews human exposure to arsenic in non occupational population, mostly through drinking water which is a worldwide problem, more so in south East Asia. Sources of arsenic, normal and abnormal levels in blood and tissues levels, old and new methods of estimation of arsenic, mechanism of action of arsenic in experimental animal is briefly reviewed. Old described clinical manifestation of arsenic in humans is briefly reviewed and newly described clinical manifestations in human with special emphasis on atherosclerosis, liver and diabetes are discussed. Proposed biological mechanisms in experimental animals included up regulation of inflammatory signals like cytokines and TNF-α, oxidative stress, hypomethylation, decreased DNA repair and apoptosis, cell proliferation, angiogenesis, activation of several enzymes like methyl transferase which converts inorganic arsenic to MMA and DMA, and GSH in in-vivo and in-vitro in experimental rat liver slices. Experimentally NAC (N-Acetyl Cysteine) treatment attenuates oxidative stress in atherosclerosis apoptosis and liver injury. GSH probably plays an important role in deactivation of the intermediate products of arsenic metabolism and prevents peroxidation of membrane lipids.

Chronic human exposure has been linked to several systems in the human body: dermal (exfoliative dermatitis, keratosis, vitiligo, skin cancer), peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepatosplenomegaly resembling NCPF, portal hypertension, peripheral vascular disease and BFD, arteriosclerosis and cancers of lung, urinary bladder, other internal organs and diabetes. Experimental and epidemiological evidence support diabetes effect of high level arsenic exposure. Low and moderate exposure to arsenic in drinking water is widely prevalent and may play a role in diabetes prevalence and needs to be studied further. Role of arsenic in Indian arteriosclerosis, diabetes and liver diseases, (cirrhosis, NCPF), need to be studied further. Study of mechanisms and enzymes mentioned need to be studied in humans exposed to arsenic and other xenobiotics. Measuring arsenic exposure, metabolic and biologic effects by newly described and simpler urine proteomics may accelerate our understanding of arsenic on health consequences.

Introduction

Arsenic was known as a therapeutic agent to ancient Greeks and Romans.1,6-16 It has been reported that arsenic poisoning resulting from the used copper arsenic as a pigment for coloring wall papers.2 The media belief that any form or amount of arsenic is unnecessary, potentially harmful, toxic and/or carcinogenic maybe unrealistic. Recent circumstantial evidence, on the other hand, suggests that arsenic maybe an essential ultra trace element in animals.3 The foundation of many of the modern concepts of chemotherapy derived from Ehrlick’s early work with organic arsenicals. The advent of penicillin disposed off anti luetic arsenicals and other newer drugs have nearly eclipsed the use of other organic arsenicals. Currently, in the human therapeutics arsenicals are of importance only in the treatment of certain tropical diseases.3 Now, the impact of arsenic on health is more from industrial and environmental than from medicinal exposure.2 The biological, toxicological and environmental significance of arsenic have been written by several authors which have been quoted by Harvey6 and are not included in this review.

Exposure to arsenic has been linked to several diseases including arsenical dermatosis, arsenical neuropathy, cancer in different organs, liver diseases, cardiovascular, pulmonary, gastrointestinal disorders and diabetes mellitus. Evidence indicates that medical and naturally occurring arsenic favours the development of hepatic disorders including fibrosis and portal hypertension.1-15 Naturally occurring arsenic in drinking water is a worldwide health problem.16-16 It has been reported from six districts of West Bengal,6-8 Chandigarh (Punjab, India),14,15 Bangladesh, South-east Asia in Cambodia, Thailand, Vietnam etc. where millions of people are exposed to high levels of ground water arsenic and thousands have been diagnosed with arsenic poisoning.6 This was discussed in 2007 in an International Conference by Mickey Simpson and Prof Polya in Manchester, UK. It has also been reported in local areas of Taiwan, Chile (Antafagusta), Argentina (Cordoba), Mongolia, China, Hungary, and Japan (Torka).1 In the United States approximately, 13 million individuals live in areas of west, mid west and north west with a concentration of organic arsenic in drinking water. The sources of this arsenic are mostly natural and less from occupational exposure.

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Arsenic is also known to accumulate in marine organisms.2,18-20 It is estimated that about 8% of public water supply in US may exceed this limit.17 Nevens et al.,9 Basu,11 Datta,12 suspected arsenic as an etiological agent in non-cirrhotic portal fibrosis (NCPF). This has stimulated experimental and clinical research in arsenic metabolism. Rapid progress in analytical chemistry, genetics and proteomics are providing new research tools for advancing and understanding of arsenic exposure, metabolism and biological effects.

We review the sources of arsenic, normal and abnormal levels in blood and tissues, estimated arsenic requirement, newer methods of estimation, newer studies in metabolism and relation to human diseases, including atherosclerosis, liver diseases and diabetes.

**Essentiality of Arsenic**2,18-20

Arsenic deprivation has been induced in chickens, goats, hamsters, pigs and rats leading to depressed growth, impaired fertility, with increased perinatal mortality in pigeons and goats with death during lactation, decreased serum triglycerides, myocardial damage; arsenic deprivation may also lead to changes in mineral concentration in various organs and kidney calcification in rats with high calcification inducing diets.2 These findings suggest that arsenic may be an essential ultra trace element in animals.2,18-20

The circumstantial evidence of arsenic essentiality in humans is only limited.19 Injuries of the central nervous system (CNS), vascular disease and cancer in humans are reported to show decreased serum arsenic concentration.2 It is a major clinical nutritional concern in humans as both low (< 12 µg/day) or high (more than 250 µg/day) intake possibly induce susceptibility to cancer of urinary bladder, kidney, liver, skin, lung.2

**Sources of Arsenic**1-3,5,6,17,21-31

**A. Soil, Vegetation, Water**

Normally, arsenic occurs in air (0.02 µg/m³), natural water (0.05 mg/L), soil (0.05 mg/L), vegetation, plants and forests (3-5 mg/Kg). Depending on geographic locations mentioned above, it is much higher. Airborne elements are high in dust storms (0.5 to 2 ng/Kg), in volcanic dusts (300 to 800 ng/Kg), in wild forest fires (0.5 to 4.4 ng/Kg), in snow 10-20 pg/Kg) and in sea salt sprays (0.1 to 0.6 ng/Kg). It is high in metal rich soil (250 to 2500 ng/Kg). It is also high in some water supplies in Latin America (0.8 mg/L), in Western Pacific (2.34 to 0.9 mg/L), in shallow tube wells 24 to 36 m deep (0.06 to 0.58 mg/L) and 1.5 mg/L in an open drain near a chemical factory in Calcutta.

Arsenic is also known to accumulate in marine organisms such as fish, clams, shrimps (50 to 100 µg/Kg and more), of this element. Sea food contains organic arsenicals (arsenobetaine), arseno-sugars and arsenolipids. Marine products usually contain organic arsenic (arsenobetaine) in higher concentrations, is non toxic and is excreted unchanged.15 Organic arsenic was detected in shrimps as early as 1935 in amounts of 43 to 174 µg/Kg.1 The biotransformation and toxicity of inorganic and organic arsenical compounds differ significantly. Inorganic arsenic compounds (arsenites, arsenates) are metabolised in liver to mono-methyl (MMA) and dimethyl arsenites (DMA) and excreted in urine together with unchanged organic arsenic (ASi).3 Excess arsenic in artisan well water in Taiwan is reported to result in Black Foot Disease (BFD), arteriosclerosis, hypertension and increased incidence of cancer of skin and lung.29-30

**B. Industry:**

Besides soil, vegetation and drinking water, industries also contribute to higher levels of arsenic such as occupational exposure in wine growers, mining industry, smelters (USA), coal mining,20 (China), manufacturers of insecticides, herbicides, rodenticides, pesticides, components of certain glass alloys, semiconductors etc.1 In 1900, in Manchester and Liverpool some 7000 cases of subacute arsenic poisoning and 70 deaths were attributed to the consumption of beer containing more than 15 mg/L of arsenic.1

**C. Medications:**

Old arsenicals like antipsoriatic Fowler’s solution (arsenites), antiluetics like Neoarsphenamine, Acetylarsan and arsenoxide for tropical Eosinophilia are nearly obsolete. However, there are increasing reports (particularly from some Western countries) about alternative medical therapies like herbal, ayurvedic and unani medications as a source to arsenic toxicity in humans from home made brews.12,14,15

**Absorption of Arsenic**

Salts of arsenic are readily absorbed from the gastrointestinal tract but elemental arsenic is not. Arsenic is also absorbed through the lungs and skin. After absorption, inorganic arsenic is in liver, spleen, kidney, lung and gastrointestinal tract.1,3 It is readily cleared from these tissues but leaves residues in keratin rich tissues like hair, nails and skin.1,3

**Normal Tissue and Blood Levels**6,10,17,33-34

Human serum arsenic levels as measured by atomic absorption spectrometry in Bombay are less than 0.02 µg/mL.1,32-34 Normal urinary excretion of arsenic is 2 to 25 µg/day. The median urine level in 788 US adults of total arsenic was 7.1 µg/L, of dimethyl arsenate of 3.0 µg/L and 0.9 µg/L of arsenobetaine.17 Concentration of arsenic in hair was 0.15 ± 0.35 mg/kg, in nails 0.34 ± 0.25 mg/kg and in liver 0.16 ± 0.04 mg/kg.6,10

**Daily Requirements**

The normal average adult dietary intake – through ingestion worldwide may be up to 17 to 60 µg/day. Estimated intake in the USA varies from low 8.4 to 30 µg/kg.2,26 Cereals, seafood, fish, algae etc account for this. This may vary with type of soil, water and environment. Of this only about 5% is absorbed (daily 50 µg). According to Schroeder 28 of intake of 1000 µg/day – 900 µg/day are excreted in faeces, 50 µg/day in urine, 5 µg/day in hair. Absorbed intake of arsenic is retained in liver, kidney, skin; daily retention may be 4 µg. The total body content is about 8 mg. The daily requirement of arsenic varies between toxicologists and nutritionists. Based on animal data, human requirement is estimated to be 10-25 µg/Kg.2 An amount of exposure (a Reference Dose, RD)7 likely to cause an adverse effect of 0.3 mg/Kg for a 70 kg person is suggested. Nutritionists have suggested that the upper limit of arsenic intake could well be 140 to 250 µg/Kg.2

**Toxicity and Metabolism — Experimental Studies**3,10,13,36-43,45-47

Since this article is mainly for practicing physicians and since
the pathophysiological events after human exposure to arsenic (both acute and chronic) are difficult to discern in humans and since mechanisms of arsenic toxicity are rarely discussed in clinical papers, recently undertaken experimental studies are briefly reviewed.

Arsenic occurs in three forms: Neutral (Zero valence), Trivalent and Pentavalent. For chemical convenience, arsenicals are grouped into organic and inorganic compounds. Inorganic arsenicals differ from organic compounds in several important pharmacological aspects. Nearly, all trivalent inorganic arsenicals can be regarded as salts of metaarsenous acid various salts of arsenates and arsenites are used in insecticides, rodenticides, fungicides, herbicides and detoxicants. Organic arsenicals, on the other hand, are derivatives of benzene arsenic acid. Some of these pentavalent arsenical derivatives are used in medicine in hog and chicken, the pentavalent arsenicals (all of which manifest anionic character in body fluids) appear to penetrate the cells of the host less than the cells of the parasite and thus, have a higher therapeutic index than the trivalent form. Regardless of whether an arsenical is introduced into the body as trivalent or pentavalent arsenical, all major toxic and antimicrobial action are usually attributed to trivalent form. The major toxic action of arsenicals in parasite and the host is inhibition of sulfhydroxyl (SH) enzyme. This is well reviewed by Harvey. In general, inorganic arsenic is more toxic than the organic and trivalent arsenic is more toxic than pentavalent and zerovalent arsenic. Arsenic in topsoil is exposed to atmospheric oxygen and is usually present in pentavalent form. Industrially produced arsenic is in the more toxic trivalent form.

In mammals arsenic is mainly metabolized in the liver and to some extent in kidneys, Proposed mechanisms include hypomethylation, up regulation of inflammatory signals, enhanced oxidative stress, alteration in signal transduction pathways, induced cell and cytokines including TNF α, IL-6, reduced glutathione homeostatins, lipid peroxidation, protein oxidation, reduced DNA repair, angiogenesis and apoptosis. Besides usual liver enzymes several other enzymes like methyltransferase, coproporphyrinogen oxidase (for arsenic induced porphyrin urea, enzymes related to glutathione (GSH), homeostasis, MDA for lipid peroxidation, glutathione GSH regenerating enzymes, scavenging enzymes, and Catalase. Proportion of arsenites and arsenates were studied in mice models. Possible mechanisms related to various doses of arsenic (0-6 mg/Kg) were studied in male mice, mice liver homogenates were used to study mitochondrial oxidative stress, mitochondrial permeability transit (MPT). Apoptosis was studied by Tunnel stain and histology was studied. This is besides measuring mouse serum ALT and urinary excretion of arsenic.

These studies suggest that the antioxidant system in the liver of mice is activated at 2 months after exposure but prolonged (4 months) exposure to arsenic probably causes “overuse failure”. Liver arsenic content after prolonged exposure was high inspite of increased urinary excretion confirming “overuse failure”. Oxidative methylation and reduction (detoxification) produces reactive oxygen species (ROS) which induce cytotoxicity, necrosis and apoptosis. Rat liver, like human liver, inactivates inorganic arsenic to MMA and DMA acids which excrete in urine along with unchanged inorganic arsenic (ASI). ASI a dose dependant reduction of hepatic glutathione (GSH) greatly modifies the metabolism of inorganic arsenic in vivo; it proportionately impairs methylation of inorganic arsenic and also impairs kidney excretion. This study demonstrates the role of GSH in the metabolism of inorganic arsenic in-vivo.

After feeding 8 mg/Kg of arsenite mouse ALT was raised 3 to 5 times and mouse liver showed toxicity characterized by fatty infiltration/degeneration and infiltration of blood cells in spaces of Disse. Apoptic changes in hepatocytes with increase in Caspase 3 (not Caspase 8). Caspase 9 was activated remarkably indicating involvement of mitochondrial apoptosis. Mitochondrial permeability transit (MPT) was found to be related to increased oxidative stress from arsenic leakage of cytochrome C in the cytosol which correlated with MPT and apoptic death.

These studies thus showed oxidative stress, hypomethylation and reduced glutathione (GSH) as a cause of hepatic toxicity which can be prevented by N-Acetyl Cysteine (NAC-GSH donor).

**Arsenic Exposure in Humans and Clinical Manifestations**

In order to avoid duplication they are taken together. Because of widespread exposure and multiple health consequences, there is now better understanding of the mechanisms involved in arsenic toxicity in human populations. In non occupational populations arsenic exposure occurs mostly through drinking water while in occupational settings exposure mainly occurs via inhalation. Some of these are discussed below:

**Acute Toxicity**

Because inorganic arsenical medications are becoming obsolete and use of organic arsenicals nearly so, iatrogenic arsenic poisoning is now rare. Further, the use of accidental, homicidal, and suicidal arsenic poisoning is greatly diminished. The acute toxic dose of an arsenical varies greatly depending on the compound and the physical form. The acute chemical effects in arsenic poisoning vary whether the arsenic is taken in as an organic or inorganic compound. Symptoms may appear very early or may be delayed (10 to 12 hours).

**Gastrointestinal Symptoms: (Acute and Chronic)**

Initially, after ingestion, sharp crampy abdominal pain, vomiting and diarrhea is reported. Acute arsenic poisoning from ingestion results in increased permeability of small bowel vessels, inflammation, and necrosis of the intestinal mucosa. These changes result in severe hemorrhagic gastroenteritis which may be associated with cardiovascular collapse. After injection of organic arsenicals also nausea, vomiting, headache malaise and occasionally collapse from allergic idiosyncratic reaction may occur. With chronic arsenic exposure, anorexia, nausea, vomiting, recurrent diarrhea and pain in abdomen may be seen. Consideration of drugs and toxins play an important role in the differential diagnosis of acute abdomen.

**Chronic Exposure**

Chronic exposure to arsenic has been linked to several systems in the body and are discussed briefly as such:

**Hepatic**

Sporadic reports of liver involvement following intake of inorganic arsenicals in medicinal forms (Fowler’s solution) are available. Arsenic contamination of drinking water was suspected to cause NCPF and portal hypertension in India. Santra et al, have studied hepatic abnormalities in 248 clinic patients (195 men) with clinical evidence of chronic arsenic toxicity who had been exposed to arsenic contaminated drinking water for up to 15 years. Twenty-three control subjects from the same area who were exposed to arsenic-free water for 12 years.
were also included. Of these 248 patients, 77% had hepatomegaly, 20% splenomegaly, ascites 2%, ‘rain drop’ pigmentation of skin in 94%, keratitis in 65%, anemia in 44%, cough in 67%, and dyspnea in 62%. The incidence of hepatomegaly was found to have a linear relationship proportional to increasing exposure to arsenic in drinking water in both sexes. Liver profiles in 93 patients with hepatomegaly revealed elevated ALT in 26%, elevated AST 61%, elevated S. Alkaline phosphatase in 29% and elevated S. globulin in 21%. Arsenic content in the liver in 29 cases was mean 1.46 mg/Kg, maximum 6.0 mg/Kg, control 0.16 ± 0.04, p < 0.001. It was undetected in 6 of 29 samples. Liver biopsy was done in 69 cases. Liver histology showed portal fibrosis in 63 (91.3%), cirrhosis in 2 (2.9%) and normal in 4 (5.8%). Both patients with cirrhosis were positive for HBsAg. The degree of fibrosis was Grade I in 54%, Grade II in 80%, Grade III in 90% and Grade IV in 6%. Thus, the degree of fibrosis in the liver in most cases was mild. Of 73 cases, esophageal varices were found in only 5 cases. Thus, majority of patients had no endoscopic evidence of portal hypertension, though portal zone fibrosis was seen in liver biopsy in most of these. Patients with arsenicosis and splenomegaly showed evidence of increased intrasplenic pressure (30 to 36 cm saline) suggesting portal hypertension. Splenopancreatography in these patients showed intrahepatic portal vein obstruction. The features of portal fibrosis and multiple vascular channels in expanded portal zone observed by these workers as well as by others, is similar to that observed in NCPF or idiopathic portal hypertension.6-8,13

Non-Cirrhotic Portal Fibrosis (NCPF)6,9,11,12,14,15,49

Guha Mazumdar49 has summarized the history of NCPF in Bengal and rest of India and summarized the relation between NCPF and arsenic exposure: These workers and others, as stated above, also found in NCPF patients (exposed to increased arsenic contaminated water), an increased levels of arsenic in serum, hair, nails and liver tissue.49 Reviewing this, Boyer44 suggested exposure to enteric parasites and toxins, metallotoxicity resulting in collagenosis occurring in perinsusinal and peripheral region with portal hypertension, suggesting etiopathogenesis of NCPF to be multifactorial.44 Bhawe,51 Bhivankar41 in a cosmopolitan city of Mumbai studied 40 males; 15 normal controls and 25 biopsy proved cirrhotics. As expected most cirrhotics had significant anemia, raised ESR, abnormal LFT, low serum proteins, low serum albumin, with raised serum gamma globulin and prolonged prothrombin time. Serum arsenic levels as estimated serum albumin, with raised serum gamma globulin and anemia, raised ESR, abnormal LFT, low serum proteins, low proved cirrhotics. As expected most cirrhotics had significant of Mumbai studied 40 males; 15 normal controls and 25 biopsy

pigmentation, leucomeelanosis is seen. Pigmentation may involve mucous membrane in mouth. Vernicular or nodular keratitis in palms and soles are common. Skin lesions are distributed bilaterally symmetrically mostly around scalp, the neck, in the armpits and around the nipples. In more severe cases changes in blood vessels of the skin are present and painful, swollen red extremities are seen. The fingernails show mess lines in severe cases. Impaired skin and wound healing, pyoderma and increased incidence of skin cancer are reported.50 (Carcinogenesis is discussed below). According to Guha Mazumder,13 “Field Guide to Diagnostic algorithm of arsenicosis” is based on the presence or absence of above characteristic dermatological manifestations and keratitis. Other systemic manifestations of arsenicosis are much more common in subjects with dermal arsenicosis.

CNS and Neuropathy1,2,6-13

Polyneuropathy characterized by tingling, numbness, burning soles and weakness due to involvement of multiple peripheral nerves particularly in the lower limbs is seen, and may be reversible in early stages. Weakness is due to anterior and posterior tibial group of muscle involvement. Deep reflexes are diminished or absent. Deep sensibility much more affected than the superficial tactile and thermal sensation, resemble diabetic neuropathy. It is probably unrelated to dose of arsenic. It is uncertain whether it is due to inflammation, or due to degeneration from arsenic toxicity or avitaminosis or due to immunological mechanism.31

Headache, irritability, lack of concentration, depression, sleep disorders, vertigo, weakness, cognitive and memory impairment are reported in people with arsenicosis from West Bengal who also show neuropathy. Fatal arsenical encephalitis was reported with I.V., I.M. arsenicals in older reports.3 Objective evaluation with EMG and nerve conduction studies are reported to confirm sensory motor neuropathy. Increasing incidence of cerebrovascular disease in chronic arsenicosis is reported. A significant dose – response relationship was observed between arsenic concentration in well water and prevalence of cerebrovascular disease. The biological gradient was reported more prominent for cerebral infarction.13

Cardiovascular

Small doses of inorganic arsenicals induce mild vasodilatation: large doses (acute intoxication) evoke prominent effects on the circulatory system. Injury may occur in all capillary beds but is most pronounced in the splanchic area resulting in transudation of plasma and a sharp decrease in blood volume leading to shock which may be induced or aggravated by flocculation of the plasma proteins. ECG abnormalities are reported and may persist. Rarely, a rapidly developing angioneurotic shock like reaction follows with some IV arsenicals whose use now is uncommon. Chen et al29 and Wu et al30 describe the atherogeneity and carcinogenicity of high arsenic artisan well water of the Black Foot Disease (BFD).30 in 42 villages in Taiwan.29,31 The vascular damage in BFD seems to result from an early destruction of vascular endothelial cells. BFD is a unique peripheral arterial disease characterized by severe systemic arteriosclerosis as well as dry gangrene and spontaneous amputation of affected extremities. In a series of 241 BFD cases, 169 required amputations.29 Histologically; BFD consists of arteriosclerosis obliteratorans and thromboangiitis obliteratorans affecting small vessels. It starts as coldness, numbness of feet, intermittent claudications progressing to ulceration, gangrene and spontaneous amputation. The prevalence is reported as 8.9 per 1000 in affected Taiwanese inhabitants who also get
Raynaud’s syndrome and acrocyanosis. Comparatively, the prevalence of BFD in affected persons in India, Bangladesh and Chile is low. BFD patients also have an increased prevalence of hypertension. There is dose response relationship between ingested inorganic arsenic over BFD, hypertension and mortality from ischemic heart disease. Increased risk of hypertension with inorganic arsenic exposure is reported from West Bengal and Bangladesh. In Taiwan and in Antafagasta (Chile), high exposure to arsenic over a long period has been reported to show fibrous intimal thickening of small and medium sized arteries in children and young adults. In Taiwan dose response has been reported in these patients. This may be due to other co-exposure, due to socioeconomic development, or due to dietary deficiencies of selenium and zinc or due to functional polymorphism in genes related to arsenic metabolism. Suggested potential mechanism mentioned above are: ROS, lipid peroxidation, hydroxyl radicals, altered nitric oxide metabolism and altered endothelial function up regulation of inflammatory signals, release of TNFα, cycloxygenase-2 expressions. Arsenic may induce diabetes and hypertension, atherosclerosis by enhancing arterial thrombosis and platelet aggregation. In a follow up of 15 years, a significantly higher mortality from cardiovascular disease was seen. Wu et al analyzed age adjusted mortality rates to examine the dose response relation between ingested artisan well water levels of arsenic and risks of vascular diseases among these patients. Arsenic levels in artisan well water were associated with peripheral vascular disease and cardiovascular disease in a dose response patterns but not with cerebrovascular diseases.

Navas-Acien et al in 2005 performed a systematic review of the epidemiologic evidence from 1966 to 2005 on the association between arsenic and cardiovascular outcomes. Thirty studies conducted in general populations, eight in high arsenic areas in Taiwan, five in other countries and sixteen studies conducted in occupational populations were identified and exposures was assessed ecologically in most studies. Arsenic may induce arterial thrombosis due to atherosclerosis, platelet aggregation and its exposure has been related to hypertension and diabetes. In Taiwan relative risks comparing the highest arsenic exposure category with the lower ranges from 1.59 to 4.90 for coronary disease, from 1.19 to 2.69 for stroke, and from 1.66 to 4.28 for peripheral arterial disease. In other general populations, relative risks ranged from 0.84 to 1.54 for coronary disease, 0.69 to 1.53 for stroke and from 0.61 to 1.58 for peripheral arterial disease. In occupational populations, relative risks ranged from 0.40 to 2.14 for coronary disease mortality and from 0.30 to 1.33 for stroke mortality. A dose response meta analysis was considered as inappropriate because of the heterogeneity in and methodological limitations, of the available studies. Methodological limitations, however, limited interpretation of the moderate to strong associations between high arsenic exposure and cardiovascular outcome in Taiwan. In other population or in occupational settings the evidence was inconclusive. Since low, moderate or high arsenic exposure, (as stated above), is widely prevalent, even a small effect of arsenic on cardiovascular risk, according to these authors, is potentially important and should be a research priority.

**Respiratory Diseases**

Normally, atmospheric arsenic is 0.02 μg/m³, is usually in pentavalent form. It is higher with metal smelters refining arsenic. It is also high when pesticides, weed killers, fungicides, rodenticides, insecticides are used. Most of the inorganic dusts are associated with chronic hypersecretion of mucus and/or interstitial lung fibrosis. These dusts are associated with chronic hypersecretion of mucus which leads to chronic bronchitis, with or without reduction of expiratory flow ratio, interstitial lung disease, cancer. Low concentration of arsenic have been reported in USA but high of arsenic near a gold mine and smelter is reported to produce skin and mucosal irritation. Urine analysis in all the people in the vicinity of copper mines in Chile showed significant absorption. Children living near a power station in Czechoslovakia showed anaemia and an increased amount of arsenic in hair. Coal burning in China is reported to show higher air concentration of arsenic.

Non malignant lung disease (chronic bronchitis, bronchiectasis, and interstitial lung disease) has been reported in epidemiological studies from Antafagasta Chile, Bangladesh and West Bengal in subjects exposed to drinking water containing arsenic and dermal manifestation of arsenicosis. Chronic cough was reported in 38 to 57% of subjects. Chronic cough was more common in males, and could be with or without expectoration. Lung function tests showed features of both restrictive lung disease and combined obstructive and restrictive lung disease. Both forced respiratory volume in one second, forced vital capacity (FVC), and adjusted FVC were reduced. Thus, over and above respiratory symptoms, consumption of arsenic contaminated water in men was found to be associated with reduced pulmonary function. In subjects with chronic cough of 2 or more years and dermal manifestations of arsenicosis, contrast-enhanced computed tomography (CECT) showed bronchiectasis in 67%. This study showed that drinking of high arsenic contaminated water was associated with increased incidence of bronchiectasis in men.

**Carcinogenicity and Terratogenicity**

Numerous epidemiological cohort and case control studies suggest association between chronic arsenicosis and incidence of skin cancer. Chen et al, Liu et al and Wu et al analyzed age adjusted mortality rates and dose response relation between artisan well water arsenic levels and the risk of cancer in 42 villages in Taiwan. A significant dose response relation was observed between arsenic levels in walisian well water and cancers of urinary bladder, kidney, skin and lung for both males and females and cancers of the prostate and liver in males. Tello studied carcinomas of the internal organs and their relationship to arsenic contaminated drinking well water in the Republic of Argentina: of 340 patients skin lesions — deep basal cell carcinoma in 276, superficial basal cell carcinoma in 130, squamous cell carcinoma in 239, Bowen’s disease in 113, mixed carcinoma in 13, carcinoma of internal organs 15%, carcinoma of lung in 34, carcinoma of larynx in 8, carcinoma of stomach in 3, carcinoma of liver in 2 and carcinoma of pharynx, trachea, esophagus and breast 1 each. Thus, basal cell carcinoma predominated over epithelial lesions. Skin cancers might arise in non-keratotic or keratotic areas of the trunk, extremities or hands. These may be single or multiple may appear as erythematous, pigmented crustaceous, fissured, nodular, ulcerated or eroded. Gerhardson et al in a study of multiple elemental assay of tissues of diseased smelter workers (n=85) and normal urban controls (n=15) found significantly higher levels of arsenic and other elements in smelter workers lungs as compared to normal controls (n=15). In urban areas higher levels of arsenic were observed among all smelter workers as compared with 10 controls. The increase in arsenic was six-fold. These authors concluded that the lung cancer in smelter workers may be multifactorial.

**Diabetes Mellitus**

Exposure to high levels of arsenic in drinking water in Taiwan...
and Bangladesh is reported to be associated with increased risk of diabetes. Environmental toxicants including arsenic have been suggested to play an etiological role in diabetes development. A dose-response relation between cumulative arsenic exposure and prevalence of diabetes mellitus was observed in Bangladesh. Prevalence was increased in subjects with keratosis. This is based on epidemiological studies on long term exposure to drinking arsenic contaminated water. However, repeated long term sampling for arsenic in the water samples is lacking in nearly all epidemiological studies. The biological mechanism for an association between chronic arsenic exposure and increased risk of diabetes are unknown. Navas-Acien et al. in 2006 performed a systematic review of the experimental and epidemiological evidence on the association of arsenic and Type 2 diabetes in 19 in vitro studies of arsenic and glucose metabolism and in 19 epidemiological studies: Five studies reported that arsenic in the food with transcription factors involved in insulin-related gene expression, upstream factor I in pancreatic β-cells and peroxisome proliferator activated receptor γ in pre adipocytes. Other in-vitro studies assessed the effect of arsenic on glucose uptake, typically using very high concentrations of arsenite or arsenates. As these studies provided limited insight on potential mechanisms, these authors identified ten in-vivo studies which according to these authors showed inconsistent effects of arsenic on glucose metabolism. Finally, these authors reviewed 19 epidemiological studies (6 in high arsenic areas in Taiwan and Bangladesh, 9 in occupational populations and 4 in other populations). In studies from Taiwan and Bangladesh, the pooled relative risk estimated for diabetes comparing extreme exposure categories was 2.52 (95% confidence interval 1.69 – 3.75) although methodological problems limited the interpretation of the association. The evidence from occupational studies and from general populations other than Taiwan and Bangladesh was inconsistent. In summary, these authors felt in 2006 that the current available evidence was inadequate to establish a causal role of arsenic in diabetes.

Because arsenic exposure is, (as stated above), wide spread and since prevalence of diabetes is reaching an epidemic proportions, epidemiological studies with arsenic concentration relevant to low to moderate human exposure and appropriately assessing diabetes were considered. Navas-Acien et al. in 2008 investigated the association of arsenic exposures as measured in urine with prevalence of type 2 diabetes in a representative sample of US adults – a cross sectional study of 788 adults aged 20 years or older who participated in 2003-2004 National Health and Nutrition Examination Survey (NHANES). He had urine arsenic determination and prevalence of Type 2 diabetes across intake of arsenic. NHANES survey (2003-2004) measured for the first time total urinary arsenic and urine arsenic species in a representative samples of US population. Total urinary arsenic, dimethyl arsenite and arsenobetaine (an organic arsenic compound derived from seafood intake). Metabolic syndrome, glycedated hemoglobin (HbA1C) were estimated. The median arsenic levels of total arsenic, dimethyl arsenites and arsenobetaine were 7.1, 3.0 and 0.9 µg/L respectively. The prevalence of Type 2 diabetes was 7.7%. After adjustment for diabetes risk factors, and markers of seafood intake, participants with Type 2 diabetes had a 26% higher level of total arsenic (95% confidence interval 2.0 to 56%) and a non-significant 10% higher level of dimethyl arsenite, 95% confidence interval 2.0 to 33.0% than participants without Type 2 diabetes and levels of arsenobetaine were similar to those of participants without Type 2 diabetes. After similar adjustments by odds ratio for Type 2 diabetes comparing participants at the 80th to 20th percentile were 3.58 for the levels of total arsenic (95% confidence interval 1.18 to 10.83%), 1.57 for dimethyl arsenate (95% confidence interval 0.82 to 2.76) and 0.60 for arsenobetaine (95% confidence interval 0.35 to 1.48). After adjustment for biomarkers of seafood, total urine arsenic was associated with increased prevalence of Type 2 diabetes. This finding supports their hypothesis that low level of exposure to inorganic arsenic in drinking water (a wide spread exposure world wide), may play a role in diabetes prevalence. In contrast, arsenobetaine, an organic arsenic compound derived from seafood intake is considered non toxic. Prospective studies in populations exposed to a range of inorganic arsenic levels are needed to establish whether this association is causal.

Genitourinary

Like mesenteric vascular dilatation, arsenic may cause dilatation, leakage from renal capillaries, varying degrees of tubular necrosis and degeneration leading to proteinuria and mild elevation of blood urea, acute renal injury maybe idiosyncratic and temporary.

Pregnancy

There are few studies of arsenic exposure and effects on pregnancy. Increased rate of still births are reported from Chile, Bangladesh and West Bengal. High concentration of arsenic (>200 µg/L) during pregnancy were reported with a six-fold increased rate of still births in 207 pregnancies in West Bengal. Reported effect of arsenic on spontaneous abortion, premature delivery and infant mortality are variable. These few studies are in women exposed long term to arsenic in well water who became pregnant while exposed. Actual quantitative exposure to arsenic during the term of pregnancy is rarely reported.

Others

Chronic arsenic toxicity is associated in the final stage with digestive complaints of frequent vomiting and diarrhea. In a late stage of intoxication, conjunctival redness, laryngitis and bronchitis are common. As stated above, anaemia has been reported from West Bengal in about 45% of subjects exposed to arsenic contaminated drinking water.

Complications

As mentioned above, exfoliative dermatitis, keratosis, vitiligo, skin cancer, peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepatosplenomegaly resembling NCPF, peripheral vascular disease and BFD, diabetes, arteriosclerosis and cancers of urinary bladder, lung and internal organs.

Diagnosis and Estimation of Arsenic

As mentioned above, any person with dermal manifestations of pigmentation, melanosis and keratosis should be suspected to have arsenicosis. Any history of exposure to known source of arsenic in atmosphere, soil, water, medications may help. Once suspected, arsnesis is confirmed by laboratory methods.

Arsenic in biological specimens is estimated by mass spectrometry, Neutron Activation Technique, Emission Spectroscopy and most practically like us in Bombay by hydroxide generated atomic absorption Spectrometry.

Urinary arsenic estimation has been used since nineteenth century. New techniques to identify methylated species in urine by Braman and Foreback expanded our knowledge of arsenic metabolism and toxicity in humans and made possible to differentiate inorganic from organic arsenic exposures.
since organic arsenicals from seafood have little or no toxicity. Exposure of arsenic and its metabolites in urine is perhaps a fluid of choice as other biomarkers like nails, hair, blood or saliva poses a technically difficult problem.\textsuperscript{60} Recently the urine proteomics to identify a decrease in B-defensin -1 in men is advocated in populations exposed to high arsenic levels.\textsuperscript{65-66} The availability of biomarkers of exposure, metabolism and biological effects may add to our understanding of arsenic health consequences and may add to our research tools. At present arsenicosis could be confirmed by high serum or tissue total arsenic by atomic absorption spectrometry and high urinary total arsenic and its metabolites.

### Prevention of Arsenic Toxicity

"Prevention is better than cure". Awareness of arsenic toxicity by the medical personnel is important. Anybody presenting with above described symptomatology should be suspected. Once suspected and confirmed, the source of arsenic toxicity is searched in clinical history and in environmental history. Use of inorganic arsenicals for suicidal, homicidal or medical purposes should be sought. With near obsolete use of organic arsenicals (except in tropical diseases), environmental factors have become more important. With globalization and migration of Indians to many countries, NRI as well as local Indian population still use unstandardised alternative therapy medicine such as herbal, ayurvedic homemade brew, unani etc.\textsuperscript{14,15} These medicines when analysed are reported to show higher than permitted level of arsenic. In above mentioned endemic areas in India, in Southeast Asia, arsenic contaminated surface water, or water from shallow tube wells, artisan tube wells, industrially contaminated water should be avoided. Harvested surface water without arsenic may be used. High protein diet particularly in poor, malnourished people may help excretion of body stores of arsenic. Supplements of antioxidants, Retinol, vitamin C and E may help poor people.\textsuperscript{6,13}

### Treatment – Chronic Toxicity

Once the diagnosis of arsenic toxicity is confirmed and once the source is determined and eliminated, treatment is considered. The aim of treatment is relief of symptoms, reduction of body stores of arsenic and reduction of the complications, particularly dermatosis, neuropathy, BFD, hepatic toxicity and cancer. The earlier the treatment is started, the better. Treatment is not successful in severe manifestations of polynuropathy, chronic liver and lung disease, swellings of the hands and legs – feet, hearing or visual defects.\textsuperscript{6} Chelating therapy is specific for arsenic toxicity.\textsuperscript{6} d- Penicillamine, 250 mg 3 or 4 times a day for fifteen days. Dimercapto succinic acid (DMSA) sulfonates 100 mg – 3 or 4 times a day for every alternate week for three courses. British Antilewiside (BAL D-S 2: 3- dimercapto propanol, 40 mg in peanut oil intra muscularily – three times a day. A total dose of 2000 to 4000 mg. All these drugs are costly and not so readily available in India. Further, they are toxic; hence, patients receiving these drugs should be monitored closely for any side effects. The use of these drugs for short periods (15 days) may show improvement in some cases, but may not prevent complications. There is no data on cancer prevention.\textsuperscript{6} Use of NAC in humans exposed to arsenic and/or other xenobiotics needs to be studied.

### Summary

Human health in the past and presently is influenced by the amount and proportion of chemical elements to which humans are exposed. This article reviews human exposure to arsenic. In the non-occupational population, arsenic exposure occurs mostly through drinking water in Ganga Brahmaputra basins in India, Bangladesh and in the basins of Mekong delta in south East Asia, while in occupational settings exposure mainly occurs via inhalations. Because of widespread exposure and multiple health consequences, and with rapid progress in analytical chemistry, genetics and proteomics, there is now better understanding in the mechanisms involved in arsenic exposure to human population.

This article reviews sources of arsenic, normal and abnormal levels in blood and tissues, old and newer methods of estimation; metabolism of arsenic in experimental animals is briefly reviewed, clinical manifestations of arsenic exposure are reviewed with special emphasis on atherosclerosis, diabetes and liver. Proposed biological mechanisms included up regulation of inflammatory signals like cytokines and TNF-\(\alpha\), oxidative stress, hypomethylation, decreased DNA repair and apoptosis, cell proliferation, angiogenesis, activation of several enzymes like methyl transferase (which converts inorganic arsenic to MMA and DMA) and GSH are reviewed in in-vivo and in-vitro in experimental rat liver. Some of these mechanisms are also considered in the etiopathogenesis of arteriosclerosis and diabetes. A reduction of hepatic GSH greatly modifies the metabolism of inorganic arsenic and impairs the kidney excretion. The liver possesses an antioxidant defense system that removes free radicals, superoxide and peroxide generations within the hepatocytes. GSH plays an important role in detoxification of the intermediate products of arsenic metabolism and prevents peroxidation of membrane lipids. GSH is required for reduction of arsenic V to arsenic III species, methylation of inorganic arsenic and thus protect cells against some effects of more toxic arsenic forms. The antioxidant defense system in the liver of mice is activated after exposure to arsenic for 2 months. However, prolonged (4 months) exposure to arsenic probably cause overuse failure of the defense systems which may result in increased accumulation of arsenic in liver and initiation of biochemical injury to the liver. N-acetyl cysteine (NAC), a sulphhydryl group donor, serves as a precursor of GSH synthesis and inhibits formation of extra cellular reactive oxygen intermediates. Experimentally NAC treatment attenuates oxidative stress in mitochondria, apoptosis and liver injury to increasing doses of arsenic exposure.

Experimental and epidemiological evidence supports diabetes effect of high level arsenic exposure. Low level arsenic exposure to inorganic arsenic in drinking water may play a role in diabetes prevalence. Since low or moderate exposure to arsenic is widely prevalent in the world, even a small effect of arsenic is potentially important from a public health aspect. Other potential mechanism to be studied include arsenic influence on the expression of gene transcription in diabetes and other diseases.

Subjects with dermal manifestations and/or keratosis should have serum arsenic and urinary arsenic and its metabolites estimation for confirmation of arsenicosis.

Besides high exposure areas to arsenic in Taiwan and Bangladesh, where association to diabetes and arteriosclerosis are reportedly common, other areas of medium or high exposure areas (mentioned above) need to study prevalence of arteriosclerosis, diabetes and liver involvement. Role of arsenic in Indian arteriosclerosis, diabetes and liver diseases, cirrhosis, NCPF, need to be studied further.

Study of several enzymes mentioned and others need to be
studied in humans exposed to arsenic and other xenobiotics. Measuring arsenic exposure, metabolism, and biological effects by newly described and simpler urine proteomics may accelerate our understanding of arsenic on health consequences.

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