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REVIEW

Inorganic arsenic: A dangerous enigma for mankind

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Human beings have been using inorganic arsenic for a long time. Many reports on arsenic poisoning have been published: eg case reports, examination reports, *post mortem* reports, and epidemiological studies. Several aspects and features of arsenic poisoning are discussed in this report. Methods of inferring arsenic-related disease, disease classification according to acute or chronic criteria, exposure route, interaction, confounding factors, and the oxidation state of arsenic are all discussed. The effects of arsenic are classified into skin, respiratory system, gastrointestinal tract, liver, cardiovascular system, nervous system, and bone marrow effects. Carcinogenicity is an important chronic effect of arsenic poisoning, so special attention is paid to it in this review. In Japan, there have been many incidents of arsenic poisoning. In this review, we often use data from these cases, such as the Morinaga powdered-milk poisoning case, the Ube soy-sauce poisoning case, the Toroku mine incident, and the Nakajo well-water poisoning case. We emphasize here the necessity of planning follow-up studies and total health care for patients exposed to arsenic.

Keywords: Inorganic arsenic, cancer, case report, acute, chronic, interaction, inhalation, ingestion, confounder

INTRODUCTION

Arsenicals are well known as poisonous agents, and were a common homicidal and suicidal drug during the Middle Ages. They have been used for various purposes, such as arsenical pesticides (including insecticides, herbicides, fungicides, algicides, sheep-dips, wood preservatives, dyestuffs, and for the eradication of tapeworms in sheep and cattle), war gases, additives for some metals and glass, in semiconductor technology, and in medical drugs for humans.[1] Arsenicals are now well known as carcinogens in humans.[2] In 1786, Fowler created the solution named after him and this contains 1% As_2O_3. This solution has since been used for treatment of such different diseases as leukaemia, psoriasis, bronchial asthma, rheumatism, diabetes, epilepsy and so on.[3] Arsenicals are also discharged in the process of smelting non-ferrous metals. Some arsenicals are naturally contained in underground water and foods.[1] A fatal dose of acute ingestion of arsenic trioxide is believed to be about 120 mg[4,5] or 70–180 mg.[6] We now discuss two famous episodes of arsenic poisoning.

In 1901, Reynolds reported clinical findings in over 500 patients whom he personally had followed.[7,8] For many months, these patients had been drinking 2–16 pints (1.1–9.1 dm^3) a day of beer which was contaminated by arsenic contained in glucose. After Reynolds' report, an investigation clarified that the number of poisoned patients was more than 6000 and that at least 70 people died. Reynolds described his examinations in detail. Digestive symptoms, catarrhal symptoms, neurological signs and symptoms, left-side heart failure with severe peripheral edema, dermatological signs, and other symptoms and signs were observed. However, no follow-up study on the incident was reported after 1901.

In 1955, an incident of powdered-milk poisoning occurred in Japan.[1,9] A large number of babies received a formula made from powdered milk contaminated with arsenic. In western

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Japan, 12 131 babies were poisoned as a result of the consumption of 'Morinaga Dry Milk', and 130 of these babies actually died as a result of this poisoning. The arsenic contained in the milk resulted from poorly purified 'secondary sodium phosphate (Na_2HPO_4) used as a stabilizer in the manufacturing process for powdered milk. The observed symptoms and signs among the babies were the usual arsenical symptoms of coughing, rhinorrhea, conjunctivitis, vomiting, diarrhea, melanosis, fever, and abdominal swelling secondary to hepatomegaly. Unusual laboratory findings included anemia, granulocytopenia, abnormal electrocardiograms, and increased density at epiphyseal ends of long bones similar to the familiar 'lead line'. In 1971, Ohira *et al.*[10] and Yamashita *et al*[11] independently conducted follow-up studies of the victims. Several symptoms and signs which could be inferred to be effects of arsenic were still observed in both studies. These especially included mental retardation and other findings that suggested brain damage in the arsenic-exposed children. No cancer mortality study has been conducted yet. The reason for it may be that these victims are thought to be still too young for developing cancer.

To date, several official reports on the biological effects of arsenic have been published by Agencies, such as the National Institute for Occupational Safety and Health of the USA (1975: NIOSH),[12] the National Academy of Sciences of the USA (1977: NAS),[1] the World Health Organisation (1981: WHO)[13] and the International Agency for Research on Cancer (1980: IARC).[2] Recently, some general textbooks[4,5] on poisoning have examined clinical findings of arsenic in the nervous system, the skin, the gastrointestinal tract, the blood, the cardiovascular system, the liver and the kidneys. The authors have continued to examine patients suffering from arsenic poisoning and have conducted epidemiological studies,[14–18] referring to these volumes, texts and many reports. We present here our thinking on the clinical presentation of arsenic poisoning.

GENERAL ASPECTS OF POISONING

How to clarify the causal relationship between arsenic and disease

Case reports

Of course, case reports are not able to establish clearly the causal relationship between arsenic and disease. However, they are very useful in giving us suggestions of causality. This is especially so when the disease or the exposure is rare, here case reports are very important in collecting evidence. In cases of acute poisoning, particularly if the temporal relationship is very clear, case reports can provide evidence of a causal relationship.

Animal experiments

Hill emphasized, 'The lack of such evidence cannot nullify the epidemiological observations in man. Arsenic can undoubtedly cause cancer of the skin in man, but it has never been possible to demonstrate such an effect on any other animal.'[19] Actually, with a few exceptions, it is very difficult to clarify the effect of arsenic on humans, using animal experiments, but it is not the purpose of this paper to comment on this practice.

Epidemiological studies

These involve searching and analyzing one population with a spatially and/or temporally higher incidence rate than another.[20] When estimating causality, an epidemiological study is regarded as very important, even essential. The lack of an epidemiological study, however, does not prove that there is no causal relationship. The epidemiological study is often impossible or very difficult to carry out, financially or for other reasons, especially in cases of environmental pollution. So, in such cases, we have to be most careful to report individual cases accurately.

Since the 1960s, conventional criteria have been used in making a decision on causality, e.g. Hill's Aspects[19] and the criteria of the Surgeon General's Advisory Committee on Smoking and Health.[21] Recently, these criteria have been discussed and criticized in several reports,[22–24] which it is not the object of this paper to discuss. The authors consider that these criteria should not be used lightly because of their weakness or lack of a completely logical base.

Acute and/or chronic poisoning

Actually, the term 'subacute' is often used to describe a state between acute and chronic poisoning in classifying types of poisoning. Generally speaking, the words 'acute' and 'chronic' are used to describe symptoms and signs in humans. *In* discussing exposure to toxic substances, however, these words are often used in relation to term and dose of exposure. Such confusion might stem

from whether acute symptoms could be observed or not. In Japan, the exposure duration was two or three weeks in the soy-sauce poisoning case,[25] and two or three months in the Morinaga powdered-milk poisoning case,[9] both of which can be regarded as acute poisoning. In Toroku, arsenic was intermittently refined from 1920 to 1962.[14,17] In Nakajo, the exposure was estimated to have taken place for about five years.[16,26] These incidents of exposure might be classified as chronic. In the latter case, acute symptoms were also observed in the report made at the end of the exposure.[26,27]

If human data were divided and analyzed according to the strata of term and dose, the data for each stratum would be quite few. Such analysis does not seem to be practical. It is important to record these data accurately. Nordberg *et al.* summarized the evaluation of critical effects from a preventive point of view.[28] Accurate records can tell us the critical effect, which is the first effect recorded from arsenic exposure, and, from this, the lowest critical dosage of arsenic can be estimated.

Inhalation and/or ingestion

We can easily imagine that the effect of arsenic on humans would be quite different according to its exposure route. The three major routes are inhalation, ingestion and percutaneous absorption.[29] As mentioned under 'Effects on the skin' (below), arsenic can cause local irritation of the skin directly. Skin absorption may occur in human beings as indicated by symptoms of arsenic poisoning, and death can occur even after spillage of solutions of soluble arsenic salts on to the skin of workers.[30]

Inhalation exposure has occurred in occupational cases such as from smelters of non-ferrous metals,[31,32] farms[33] where arsenic pesticides were used, and factories[34] where they were produced. In these cases, respiratory diseases, including cancer, are clearly observable. Inhalation and ingestion often co-exist in many exposure incidents.[14,33]

Interaction

Jarup and Pershagen reported a case-control study on the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer among Swedish copper smelting workers.[35] In the paper, an interaction was observed between arsenic exposure and smoking which was intermediate between an additive and a multiplicative model, but not inconsistent with any of these models. The definition of interaction is still unclear. Usually, the additive definition or the multiplicative definition is used in considering the interaction between two substances (Table 1).[36] Rothman recommends that interaction be evaluated on an additive scale. He presents several indices of interaction in his textbook. Therefore, interaction should be measured using these indices if possible. Once interaction could be clarified by such indices, it would be very useful in public health studies. Jarup and Pershagen[35] suggested that elimination of arsenic exposure would greatly decrease the lung cancer risk among smokers.

Table 1 Hypothetical incidence rates for lung cancer (expressed as cases per 10^5 person-years) according to exposure to cigarette smoke and arsenic (modified from Ref. 36)

	Arsenic	
Smoke	+	−
+	50	10
−	5	1

Additive definition:

10 (arsenic exposure) + 5 (smoking)
= 15 < 50 (joint exposure)

There is an interaction.

Multiplicative definition:

$10 \times 5 = 50 = 50$ (joint exposure)

There is no interaction.

According to an additive definition, when the actual joint exposure rate is greater than the hypothetical exposure rate (which is the sum of the single exposure rates), an interaction to increase incidence has occurred.

The same is true of the multiplicative definition, but the actual joint exposure rate must be greater than the product of the single exposure rates to demonstrate an interaction between them.

Confounding factors

When there are potential confounding factors, it is often said there is no link between the disease and the examined exposure risk. However, this is wrong, because the examined exposure risk exists even if a true confounding factor also exists. According to the definition of 'confounding' in epidemiology, to be 'confounding' the extraneous variable must have the following three characteristics.[37]

(1) A confounding variable must be a risk factor for the disease.
(2) A confounding variable must be associated with the exposure under study in the population from which the cases derive.
(3) A confounding variable must not be an intermediate step in the causal path between the exposure and the disease.

When discussing a potential confounding factor, this definition should first be considered.

Trivalent and/or pentavalent oxidation state of arsenic (III or V)

Inorganic arsenic is often classified according to its oxidation state, III or V. Generally speaking, arsenic (III) seems to be more toxic than arsenic(V).[38] Arsenic(III) and arsenic(V), however, can be converted to each other in the human body after intake. From several studies, Squibb and Fowler concluded that symptoms of acute arsenic poisoning follow a general pattern independent of the form of inorganic arsenic given, probably as the result of the interconversion of these forms by *in vivo* oxidation/reduction reactions.[38] It is preferable to record the oxidation state and speciation of inorganic arsenic under consideration. We need not, however, insist on it; we also consider only inorganic arsenic here.

MEDICAL MANIFESTATIONS IN MAN

Effects on the skin

Hyperpigmentation (melanosis), depigmentation (white spots) and hyperkeratosis have been reported in many papers.[39–43] Combinations of these signs are often used in diagnosis of chronic arsenism (Fig. 1).[39] 'Raindrop hyperpigmentation' is also commonly encountered in these cases and occurs mainly in areas not exposed to the sun, such as the axillae and the trunk. Fierz[44] found a dose–response relationship between ingested amounts of arsenic and the incidence of hyperkeratosis in 262 patients treated for various chronic dermatoses (Fig. 2). Cebrian *et al.*[45] quantified health effects and risks derived from chronic ingestion of arsenic in contaminated water (mean arsenic concentration 0.41 ppm), comparing the signs and symptoms of chronic arsenic poisoning in two rural populations. The arsenic was present mainly in its oxidation state V. In the exposed population, 21.6% showed at least one of the cutaneous signs of chronic arsenic poisoning, but there was none in the control group. A recent study[46] describes 67 individuals exposed to 200 μg dm^{-3} (ppb) and more of arsenic in drinking water, virtually all of whom showed typical hyperpigmentation after as little as one year's exposure.

A relationship between the number of individuals with skin changes and their place of residence was observed around the Toroku mine refinery, which had been producing arsenic trioxide (Table 2).[47] These skin lesions often continued to be observed for many years after termination of exposure.[39] In Nakajo, the authors conducted a health examination 28 years after termination of exposure from well-water contaminated by arsenic. Out of 19 patients who had hyperpigmentation 28 years ago, 12 patients still have arsenic melanosis.[48] Nakamura *et al.*[39] estimated that some lesions were developing in dermal epithelial cells in chronic arsenic-poisoning patients in Toroku. These findings indicate that dermal signs of chronic arsenism will remain, or sometimes will develop, after cessation of exposure.

The most common lesion among smelter workers exposed to airborne arsenic is dermatitis due to local irritation in the acute phase.[49]

Bowen's disease, intradermal neoplastic changes, has been associated with arsenic exposure.[50,51] Bowen's disease may progress into squamous-cell carcinoma which causes metastasis of other organs (Fig. 3).[50,51] In Toroku, among the 53 certified patients who died, there were 26 cases of Bowen's disease. It has been reported that Bowen's disease cases constituted less than 1% of the outpatients in university hospitals in Japan.[53,54] In the present study, the prevalence of Bowen's disease was much higher.

Effects on the respiratory system

In several smelting factories, lesions of the mucous membranes in the respiratory system and perforation of the nasal septum have been observed as a result of airborne inorganic arsenic.[31,32,55,56] Lundgren[32] reported that nasal septum perforation, lesions of nasal mucosa, and rhino-pharyngo-laryngitis were found among those who had worked in the whole range of the

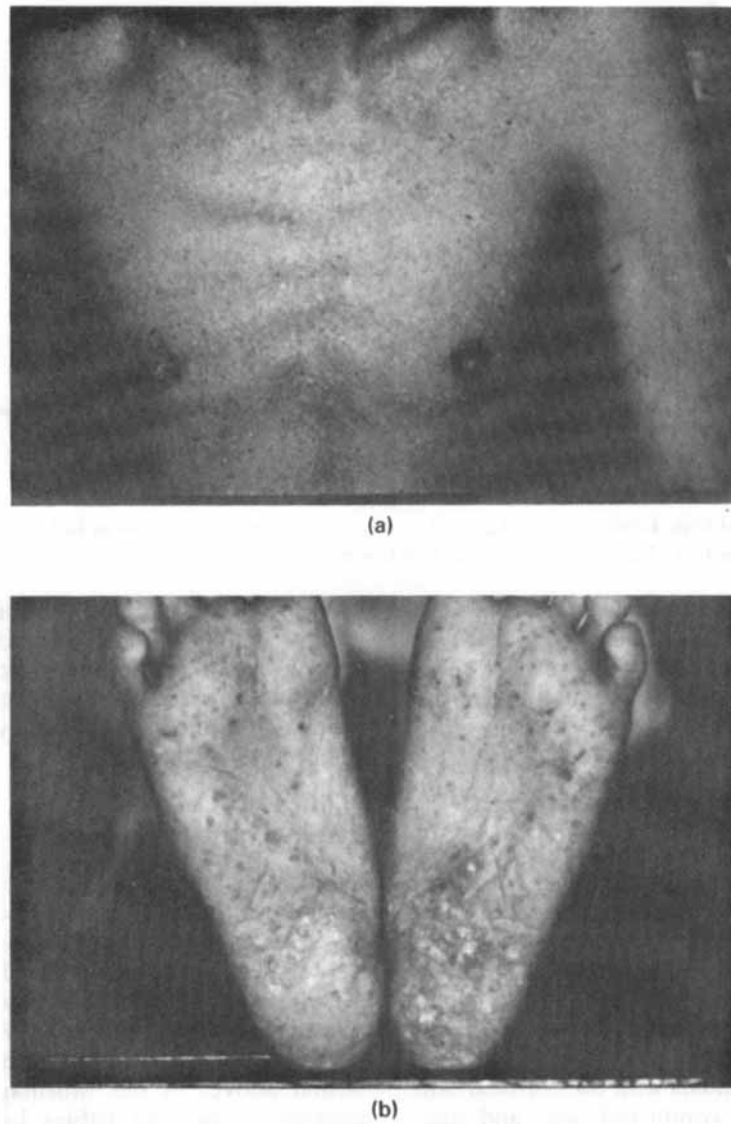

Figure 1 Skin manifestations of chronic arsenic-poisoning patient in Nakajo, Niigata Prefecture, Japan, in 1959. (a) Hyperpigmentation and white spots on the trunk; (b) hyperkeratosis on the sole. Reproduced by courtesy of Dr H. Terada, Showa University Medical School.

smelting process. Another syndrome included symptoms of tracheobronchitis and signs of pulmonary insufficiency, often due to emphysematous lesions among workers at the roasters, reverberatory furnaces, and converter halls, where mixed exposure to arsenic and sulfur dioxide took place. Nakamura *et al.*[39] documented that 54% of 48 Toroku patients had several signs of respiratory disease more than 10 years after termination of exposure. Other researchers reported almost the same results.[14, 15, 56] These results indicate that the effects often remain after the retirement of the workers.

The WHO concluded that exposure to arsenic via routes other than inhalation can affect the respiratory system.[13] Many reports suggest that ingested arsenic causes respiratory disease and symptoms in its acute phase.[7, 9, 26] In relation to this, the suspected role of arsenic as a suppressant of the immune response should be considered, because arsenic has been used as a therapeutic agent for asthma.

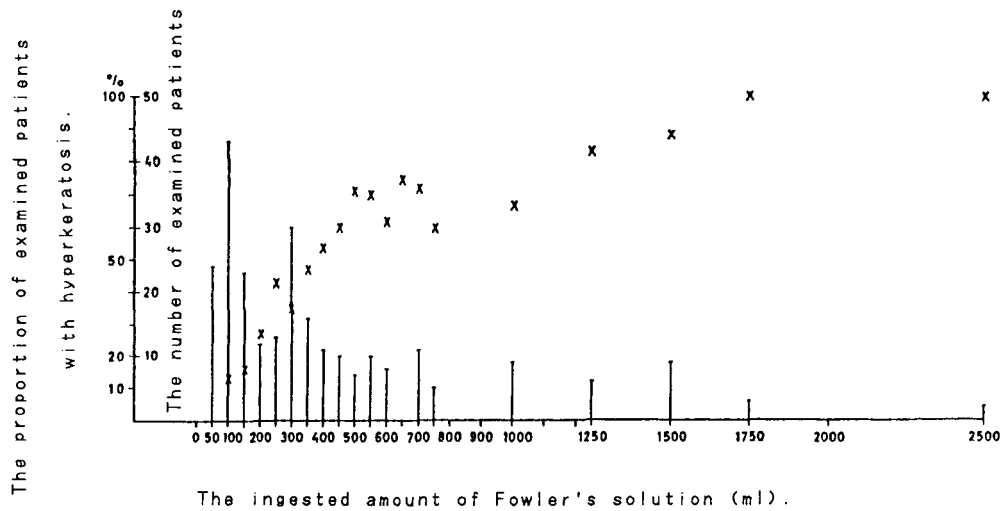

Figure 2 The proportion of hyperkeratosis according to the amount of ingested arsenic (from Ref. 44). The bars indicate the numbers of patients examined. ×, Percentage of patients with hypokeratosis.

Anosmia and atrophy of the nasal mucosa were observed in 29% (14/48) and 25% (12/48) of Toroku patients, respectively.[39] These signs seem to be the result of severe irritation by airborne arsenic compounds.[57]

Effects on the gastro-intestinal tract

In cases of acute exposure, the major lesion of arsenic poisoning is gastrointestinal damage, resulting in severe vomiting and diarrhea, often with blood-tinged stools.[13] With chronic lower-dose poisoning, from research carried out in Mexico,[45] nausea, epigastric pain, colic abdominal pain and diarrhea were more prevalent in the exposed population, and occurred more frequently in those individuals with the classical skin manifestations. Ohta conducted sex- and age-matched comparisons between former workers and non-workers in the Toroku mine more than 10 years after termination of the operation.[56] Nausea, vomiting and abdominal pain were greater among former workers. It is, however, unclear whether these symptoms, in examples of chronic poisoning, were related to damage of the gastrointestine itself or were neurological symptoms.

Effects on the liver

Abnormal findings of the serum function test, hepatomegaly, non-cirrhotic portal hypertension and liver cirrhosis have been reported.[13,25,27,31,58]

With regard to acute and sub-acute poisoning, Mizuta *et al.*[25] reported hepatomegaly and definite degenerative changes in biopsy despite only slight changes in the liver function test. As mentioned above, in the Morinaga powdered-milk poisoning case, the babies had severe hepatomegaly and icterus.[9] Also, phenomena such as edematous or hyaline degeneration of the wall of portal veins and connective tissues in the

Table 2 Relationship between the number of individuals with skin changes and place of residence, excluding those employed at the mine or smelter[a]

	Number of persons			
	Within 400 m	400–800 m	800–1200 m	Total
Those with skin changes	7	5	4	16
Those without skin changes	33	62	97	192
Total	40	67	101	208

[a] $\chi^2 = 7.33$ ($0.02 < P < 0.05$) (Ref. 47).

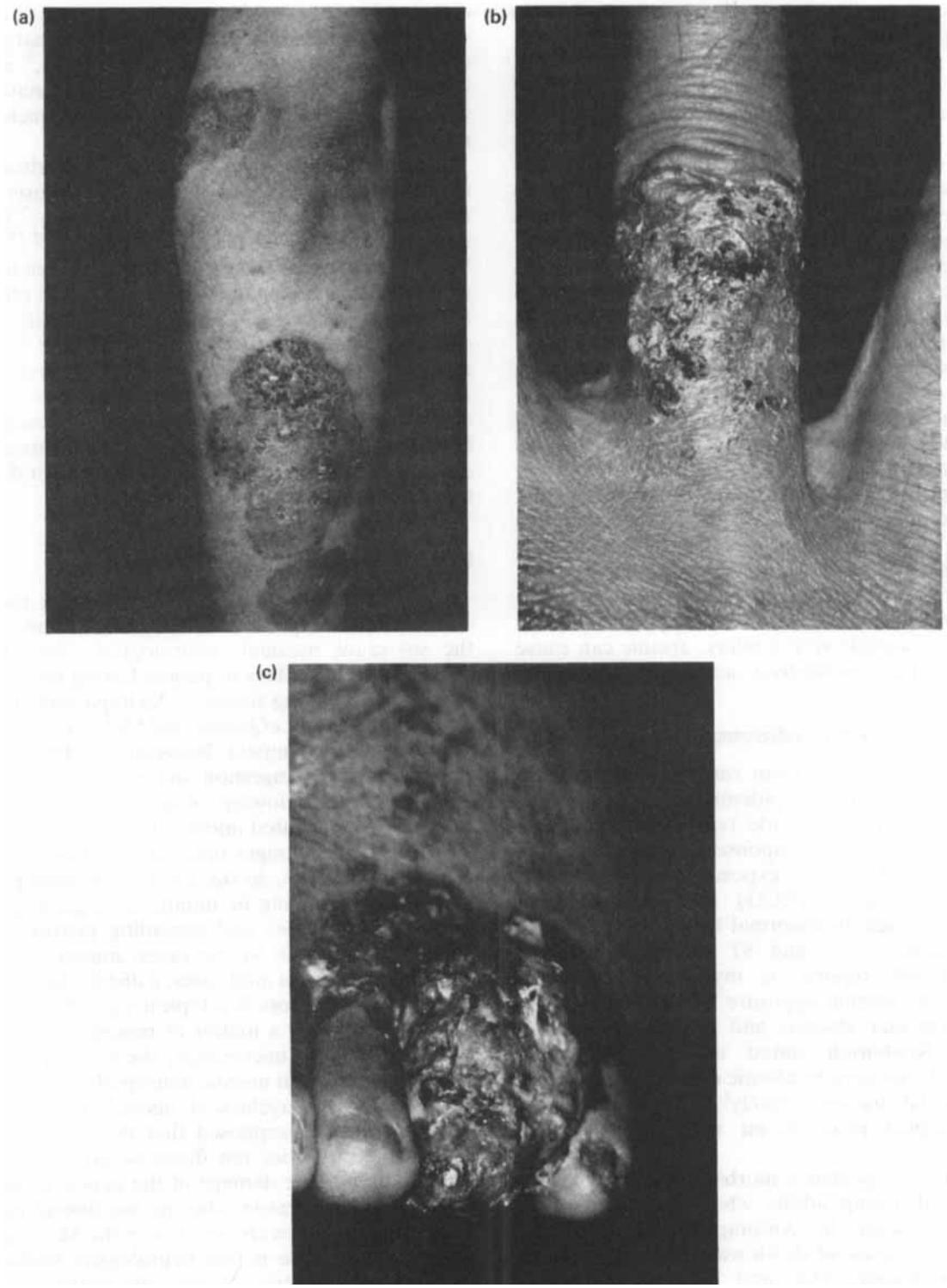

Figure 3 Bowen's disease and invasive skin cancer of a chronic arsenic-poisoning patient in Nishikawa, Niigata Prefecture, Japan. (a) Bowen's disease on the left forearm; (b) Bowen's disease on the middle finger of the right hand; (c) invasive skin cancer on the left foot. Reproduced by courtesy of Dr S. Akai, Niigata Cancer Center.

Grisson's sheaths were clearly observable in biopsy.[58]

On the other hand, in cases of chronic poisoning, liver cirrhosis among vintners is well known.[33,59] However, the possible confounding effect of heavy alcohol consumption have been pointed out. Roth[33] mentioned that postnecrotic cirrhosis among vintners is mainly caused by the hepatotoxic action of arsenic, in spite of the undeniable fact that alcohol may cause additional damage. Further information is necessary on this problem. Cirrhosis and portal hypertension were observed after medication with Fowler's solution *in* various case reports.[60–62] Terada *et al.*[27] reported that hepatomegaly was observed among 30% of residents examined in the arsenic-poisoned area in Nakajo, Japan. They concluded that liver cells can be damaged by chronic arsenic poisoning.

From these findings, it can be estimated that arsenic invades the portal area rather than the actual liver cells themselves. Therefore, damage to liver cells might be secondary. Such dysfunction of the portal area might lead to portal hypertension and liver cirrhosis. In spite of the existence of possible confounders, arsenic can cause definite effects in the liver, acutely or chronically.

Effects on the cardiovascular system

Increased mortality from cardiovascular disease was reported in two epidemiological studies.[63,64] In one of them, a crude rate ratio of 2.2 and a significant dose–response relationship over categories of arsenic exposure was obtained.[64] Electrocardiogram (ECG) changes were also reported, such as abnormal QRS, P[25], or T, QT elongation,[25,27,53,65] and ST change. There are several case reports on myocardiac infarction related to arsenic exposure.[66,67] In a review of cardiovascular disease and the work environment, Kristensen stated that a relationship between exposure to arsenic compounds and cardiovascular disease is 'likely'; however, total epidemiological research on this relationship is limited.[68]

Zaldivar reported a morbid condition of children and young adults who were exposed to dietary arsenic in Antofagasta, Chile.[69] The underlying cause of death was systemic occlusive arterial disease. Oda and his colleagues performed *post-mortem* examinations of the victims in the Morinaga milk case. They also reported disturbances of the circulatory systems including diffuse edematous or degenerative changes in the walls of blood vessels. Extreme necrotic changes of the extremities were observed in Taiwan,[70] and in the case of the vintners.[33] More information will be necessary to clarify which factors, including arsenic, lead to gangrene.

Raynaud's phenomenon, which is a syndrome manifested by attacks of pallor and cyanosis of the digits in response to cold or to emotion,[71] has been reported in several poisoning cases.[72,73] In Nakajo, many residents in the poisoned area told us in 1987 that Raynaud-like symptoms had often been observed in 1959. However, we could not confirm this quantitatively. Lagerkvist *et al.*[74] examined the vasospastic tendency and excretion of arsenic-affected smelting workers. The data indicate the peripheral vascular disturbances caused by arsenic are dependent on long-term arsenic exposure and are independent of short-term fluctuations in arsenic exposure.

Effects on the nervous system

Peripheral neuropathy appears following acute and sub-acute exposure to inorganic arsenic. In the soy-sauce incident, neurological symptoms appeared after 20 days in people having ingested soy sauce containing arsenic.[25] An important clinical point made by LeQuesne and McLeod[75] is that these symptoms appear between 10 days and three weeks after ingestion and may increase for up to five weeks following a single dose of arsenic. In chronic or repeated intoxication,[76] progression will occur over a longer interval. The first symptom is usually pain, in the form of an aching or burning, and tingling or numbness beginning in the fingers and toes and spreading proximally, over seven days. In severe cases, muscle weakness may appear. In mild cases, a distal 'glove and stocking' sensory loss is a typical sign. Recovery occurs slowly over a matter of months to years. Using an electron microscope, the major pathologic change seen in arsenic neuropathy is axonal degeneration of myelinated fibers.[77] From this finding, it can be supposed that the nerve conducting velocity does not decrease greatly even when there is some damage of the nerves caused by arsenic. The reason why the peripheral nervous system effects were very few in the Morinaga powdered-milk case is that neurological findings could not be collected because the victims were infants.[9] Hotta mentioned, in his findings on the Toroku patients, that the appearance of severe clinical polyneuropathy is quite important for

estimates of the daily arsenic intake in the exposed population.[18]

Electromyographic (EMG) examinations on exposed individuals were conducted by Hindmarsh *et al.* in Waverley, Nova Scotia, Canada. EMGs were abnormal in 33% of the exposed people, while no abnormal findings were observed among the controls.[78]

Effects on the central nervous system are demonstrated in a few case reports.[10,11,79] Especially, in the Morinaga powdered-milk poisoning case,[10,11] damage to the brain was estimated both from the follow-up findings of victims, e.g. in brain wave and mental tests, and from the theory of the blood–brain barrier.

A significant increase of hearing loss among children was reported around a power plant burning local coal of high arsenic content in Czechoslovakia.[80] In the USA, a similar study was carried out near a copper-smelting plant. However, in this case, no impairment of hearing was observed in the area.[81] In Toroku, 83% of 48 certified patients had sensorineural hearing loss more than 10 years after smelting had ceased.[39] A follow-up study of the victims of the powdered-milk poisoning reported 18% had hearing loss (>30 dB).[1] From these findings, it is concluded that arsenic can induce sensorineural hearing loss.

Several reports comment on effects on the optic nerve and the visual field.[10,30,39,81] Ohira and Aoyama reported a number of pathological eye changes in the powdered-milk group, including a case of bilateral optic atrophy.[10] As mentioned above, arsenic causes irritation of the mucosa, so conjunctivitis often happens in cases of exposure to airborne arsenic. In Toroku, 15 (31%) cases of abnormal visual field and 23 (48%) of conjunctivitis were reported among 48 patients.[39]

Effects on the bone marrow and other organs

Effects on bone marrow have been reported in many incidents.[25,27,82–84] Pancytopenia (anemia, granulocytopenia and thrombocytopenia) was observed among victims. Even in the case of chronic intoxication, similar bone-marrow suppression was observed. These effects are usually reversible within two to three weeks.[13] In the Morinaga case, hematological damage was recovered after about one month in all cases.[9]

This effect is often connected with immunosuppression, such as lowering resistance to bacterial infections.[13] Acute symptoms of arsenic poisoning often present similar symptoms to infectious diseases.[7,9,25,27] In Chile, Zaldivar supposed from his findings that dietary arsenic acts selectively as a suppressant of the immune response.[69]

Nordberg *et al.* surmised kidney damage in arsenic cases,[28] from reports of increased counts of erythrocytes and leukocytes in urine sediments. Similar findings in the autopsies in the Morinaga case might have been caused by disturbances of the circulatory systems, such as visceral hyperemia or congestion, disseminated patchy hemorrhage, diffuse endematous or degenerative changes in the walls of blood vessels, and so on.[58]

A CARCINOGENESIS IN MAN

In 1988, Hutchinson reported six cases of clinical association of skin cancer with the oral administration of arsenic compounds. In five of these skin cancer cases, arsenic was known to have been used for a long time.[85]

In 1947, Neubauer summarized 143 published cases of medical arsenical epitheliomas (half of which were skin cancer) in a review for the British Medical Research Council.[50]

In 1948, Hill and Fanig found a significant excess proportion of deaths attributable to cancer among workers producing sheep-dip powder from sodium arsenite (Na_3AsO_3). Their data suggest a relative excess of cancers of the respiratory system and skin in the factory workers.[86]

In 1953, Sommer and McManus reported in detail 27 cases of skin cancer after arsenic intake; 10 of them also had visceral cancer. All had the characteristic keratosis of the palms and soles.[87]

In 1968, Tseng *et al.* conducted a cross-sectional study on 40 421 residents of the Blackfoot-disease-endemic area in Taiwan. A skin cancer prevalence rate for those drinking well-water was 10.6/1000, which was not found in the control area. They also demonstrated a dose–response relationship between the skin cancer rate and the arsenic concentration in the water (Fig. 4).[42]

In 1969, Lee and Fraumeni compared the cause-specific mortality of 8047 white male smelting workers exposed to arsenic(III) oxide during 1938–1963 with that of the white male population in Montana State. A threefold increase in respiratory cancer was analyzed in relation to the length of employment and degree of exposure to arsenic,

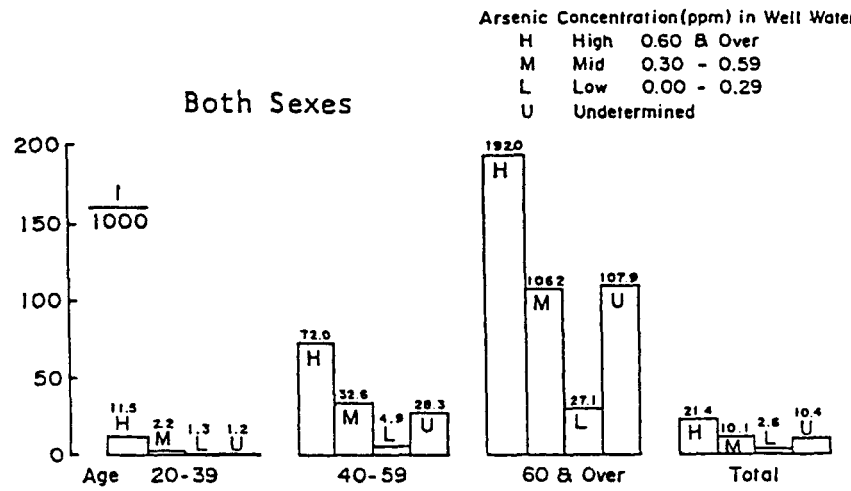

Figure 4 Prevalence rate for skin cancer in Blackfoot disease endemic area, Taiwan (from Ref. 42).

sulfur dioxide, and other elements in the smelting. Among the workers most heavily exposed, an eightfold excess of respiratory cancer was observed. This study indicated epidemiologically that inhaled arsenic is a respiratory carcinogen in man.[63]

In 1974, Otto *et al.* reported the proportionate mortality experience of 173 decedents exposed primarily to lead arsenate [$Pb_3(AsO_4)_2$] and calcium arsenate $Ca_3(AsO_4)_2$ [arsenic(V)] compared with that of 1809 decedents not exposed to those compounds. A sevenfold excess of respiratory cancer deaths was observed, compared with expected deaths.[88]

In 1985, Chen *et al.* demonstrated an ecological correlation between residence in the Blackfoot disease endemic area and cancer mortality. Standardized mortality ratios (SMRs) for cancer in this area are shown in Table 3.[89]

These studies are major steps towards clarifying the relationship between arsenic intake and cancer. Lung cancer is mainly induced from inhaled arsenic. On the other hand, skin cancer is induced from ingested arsenic.

Table 3 Standardized mortality ratios with their 95% confidence intervals for various cancers by sex in Blackfoot disease-endemic area in Taiwan, 1968–1982 (modified from Ref. 89)

		No. of deaths		Standardized mortality ratio[a]	
Cancer (ICD codes)	Sex	Observed	Expected	Ratio	95% confidence interval
Bladder (188)	Male	167	15.2	1100	933–1267
	Female	165	8.2	2009	1702–2316
Kidney (189)	Male	42	5.4	772	537–1007
	Female	62	5.5	1119	838–1400
Skin (172)	Male	46	8.6	534	379–689
	Female	49	7.5	652	469–835
Lung (162)	Male	332	103.8	320	286–354
	Female	233	56.5	413	360–466
Liver (155)	Male	305	179.4	170	151–189
	Female	146	63.7	229	192–266
Colon (153)	Male	54	33.8	160	117–203
	Female	61	36.3	168	126–210

[a] Age-specific mortality rates in Taiwan were used as standard rates to calculate the standardized mortality ratio; i.e., SMR for each cancer in Taiwan is 100.

Table 4 Classification of carcinogens by the International Agency for Research on Cancer (IARC)

Group I: Carcinogenic to humans
This category was used only when there was sufficient evidence from epidemiological studies to support a causal association between the exposure and cancer.
Group IIA: Probably carcinogenic to humans
This category was reserved for exposures for which there was at least limited evidence of carcinogenicity to humans.
Group IIB
The combination of sufficient evidence in animals and inadequate data in humans usually resulted in classification of IIB.
Group III
Not able to be classified as to its carcinogenicity to humans.

The International Agency for Research on Cancer (IARC)[2] has been discussing the carcinogenicity of various chemical substances (and industrial processes) since 1971. Arsenic was evaluated as a Group I carcinogen despite inadequate evidence in animal experiments. The IARC classification of carcinogens is shown in Table 4. This evaluation is based upon epidemiological studies of ingested arsenic for skin cancer, inhaled arsenic for lung cancer and lymphoma, and case reports of ingested and inhaled arsenic for liver sarcoma and carcinoma, leukemia, myeloma, oral cancer and colon cancer. The Environmental Protection Agency (EPA) published a *Special Report on Ingested Inorganic Arsenic* in 1988,[90] in which it offers evidence that ingested inorganic arsenic is a Class A carcinogen by the Agency's classification, resulting in an increased incidence of skin cancers, and that it may cause cancer in internal organs. These conclusions are mainly based on the Taiwanese data. The EPA points out uncertainties in the studies of the Taiwanese population, in which chemicals other than arsenic in the drinking water were not considered although they were present and may have had unmonitored effects.

Previously, we have reported excess lung cancer mortality among residents who ingested arsenic (Table 5).[16] These data seem to support the Taiwanese data in spite of the relatively small cohort size. This excess cannot be explicable by smoking habits alone. Both smoking habits and arsenic have contributed to developing cancer in the area. However, the development of cancer in this area does not fit the classic theory of cancer development—the so-called 'Initiator and Promoter' theory. Arsenic seems to be neither initiator nor promoter in this case. Recently, the concept of the 'co-carcinogen', which is understood in a wider sense than as a promoter, has been presented in a review on the carcinogenicity of arsenic.[91] This concept fits this case better than the classic one. In epidemiology, a sufficient-component-causes model[92] was demonstrated for the development of disease. By continuing to observe our cohort, a further insight might be achieved on cancer research. New models for arsenic-induced cancer are desirable. The most recent speculation on the carcinogenicity of arsenic is that arsenic may cause cancer in man through the activation of an oncogenic virus like the human papilloma virus.[91,93] Stohrer considers that this hypothesis would explain why arsenic promotes cancer of the epithelial tissues in man but not in rodents that normally do not carry the papilloma virus.[91]

On the relationship between signs of arsenism and cancer,[16] our report, and a recent review,

Table 5 Standardized mortality rate ratios for all causes of deaths, all cancer deaths, lung cancer deaths and smoking rates according to arsenic concentration of well-water in 1959 (modified from Ref. 16)

		Arsenic concentration	
Cohort (No. of residents)	Entire cohort (443)	0.05 ppm and more (189)	less than 0.05 ppm (254)
All deaths (*O*/*E*)[a]	102 (77/75.69)	120 (37/30.85)	89 (40/44.84)
All cancers (*O*/*E*)	129 (23/17.78)	235 (17/7.22)	57 (6/10.56)
All lung cancers (*O*/*E*)	404 (7/1.73)	1002 (7/0.70)	0 (0/1.30)
No. of smokers (Rate, %)	180 (40.6)	79 (41.8)	101 (39.8)

[a] *O*/*E*, Observed deaths/expected deaths.

Table 6 Classification of possible diseases and disorders for arsenic exposure among 13 Toroku patients (classified by Nagira)

1: Very definite
Dermatopathy, chronic bronchitis, polyneuritis, upper respiratory inflammation, lung cancer, bronchodilation, chronic dysekpnea, anosmia, concentric contraction of visual field
2: Quite definite
Hyposmia, chronic gastritis and enteritis (complicated gastric ulcer), concentric contraction of visual field, sinusitis, insufficiency of coronary artery (arteriosclerosis), anosmia, cerebral arteriosclerosis, multiple cerebral infarction, dementia, upper respiratory inflammation, polyneuritis, chronic rhinitis, polyneuritis (slight), sensorineural hearing loss
3: Possible
Sciatica of the right side, anemia, cochlear hearing loss, hyposmia, chronic gastritis, Parkinsonism of the left side, hypochromic anemia, gastric cancer, chronic nephritis (nephrosis), contracted kidney, renal insufficiency, nasal polyp, conjunctivitis, cerebral arteriosclerosis, arteriosclerotic cardiopathy, hepatitis
4: Somewhat possible
Cataract, abnormal liver function tests, hypertension, polyposis coli

suggest signs of arsenism or arsenical hyperpigmentation can be an indicator to infer cancer development.

A teratogenic effect is presumed from an investigation of Swedish copper smelters.[94] Research on teratogenic effects is also necessary in other arsenic-poisoning areas.

FINAL REMARKS

From the symptomatological viewpoint, Hotta divided the main clinical manifestations observed among subjects into three groups in accordance with each state of the disease as follows:[18]

(I) The initial stage: dermatitis, keratitis, conjunctivitis, rhinitis, pharyngitis, laryngitis, bronchitis, gastroenteritis.
(II) The second stage: peripheral neuropathies, Raynaud's phenomenon, hepatopathy, nephropathy, melanosis, depigmentation, hyperkeratosis.
(III) The late stage: cardio- and cerebrovascular disease, gangrene in the limbs, malignant neoplasms.

One of the authors (T.N.) is still continuing to examine arsenic-poisoning patients in Toroku after more than 10 years (the airborne exposure ceased in 1962). He has summarized qualitatively the symptoms and signs of 13 Toroku patients (Table 6). Of course, overall manifestations of chronic arsenism are not limited to these findings.

These classifications are qualitative. Now, quantitative analysis has been developed and reported in many papers. In research on diseases induced by toxic substances like arsenic, however, we have to use such qualitative evaluation of human data. This is one of the reasons why there are still many unsolved problems concerning the effects of arsenic on humans. Such research is quite different from clinical trials where the number of subjects can be varied to prevalence and relative risk.

However, in the future, it will be necessary to record and pool information to be able to analyze human data quantitatively and thereby to provide help in a risk assessment of arsenic. Multivariate analysis will also be useful, if possible, especially in identifying chronic effects. Statisticians also should be consulted in the analysis. More international cooperation will be necessary. It may well be possible to deduce the general toxicological principles of indirect carcinogens from the study of arsenic.

Arsenic is used in many places. Arsenic poisoning may continue to occur in the future. Workers and public health staff should always be aware of typical or critical signs and symptoms of poisoning as outlined by Nordberg *et al.*[28] When arsenic poisoning is found, an extension and continuation of exposure should be prevented as quickly as possible. On the other hand, effective and epidemiological investigations should also be planned.

As mentioned previously, the authors emphasize again the importance of follow-up studies and total health care for arsenic-poisoning patients. It is a matter of course that prevention is the best cure.

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