Arsenic and cancer

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Summary: Palmar and plantar keratoses developed in seven patients many years after ingestion of trivalent inorganic arsenic. Six had basal cell carcinoma (superficial multicentric type in five), carcinoma "in situ" or squamous cell carcinoma of the skin. Two had systemic carcinoma — one, bilateral breast adenocarcinoma and one, carcinoma of the colon. From these observations and from the findings of a review of the literature, there seems no question that long-term arsenic ingestion can cause palmar and plantar keratoses and skin cancer, particularly basal cell carcinoma of the superficial multicentric type, usually on the torso. It is suspected but not proved to cause other cancers.

Although over the last 50 years general exposure to arsenic has greatly decreased, particularly that from insecticides, this element is still found occasionally in drinking water (naturally or as a smelter byproduct), in certain foods and in cigarette smoke.

Résumé: *Arsenic et cancer*

Chez sept malades nous avons observé des kératoses palmaires et plantaires plusieurs années après ingestion d'arsenic inorganique trivalent. Six avaient un carcinome de la cellule basale (de la forme multicentrique superficielle chez cinq), un carcinome "in situ" ou un carcinome cutané à cellules squameuses. Deux malades souffraient de carcinome général — un d'adénocarcinome mammaire bilatéral et l'autre d'un carcinome du côlon. De ces observations et des résultats d'une revue de la littérature, on peut conclure sans conteste que l'ingestion chronique d'arsenic cause des kératoses palmaires et plantaires et des carcinomes cutanés, principalement de la cellule basale de la forme multicentrique superficielle, siégeant d'habitude sur le torse. On soupçonne l'arsenic, sans en avoir de preuve formelle, de provoquer d'autres formes de cancer.

Bien que, depuis 50 ans, le contact fréquent avec l'arsenic ait diminué considérablement, notamment en ce qui concerne les insecticides, cet élément se trouve encore parfois dans l'eau de boisson (à l'état naturel ou sous forme d'un produit de fusion), dans certains aliments et dans la fumée de cigarette.

For at least 2500 years arsenic has been used in medicine; Hippocrates, Aristotle, Dioscorides and Pliny the Elder are said to have used it. Over the past 150 years it has been an important drug: with it the physician was able to treat, with some success, dermatitis herpetiformis, asthma, syphilis, epilepsy, psoriasis, trypanosomiasis and amebiasis. These conditions, with the exception of trypanosomiasis and amebiasis, are now treated with modern, safer therapeutic agents.[1] Arsenic was also included in many medical "tonics".

The purpose of this paper is to demonstrate the correlation between long-term ingestion of inorganic trivalent arsenic (Fowler's solution; 1% potassium meta-arsenate, $KAsO_2$) and the development of malignant disease, particularly carcinoma of the skin (basal cell, "in situ" and squamous cell carcinoma), but also systemic carcinoma. We have reviewed the literature and collected results of a study of seven new cases.

Published evidence

Sir Jonathan Hutchinson, in 1887[2] and 1888,[3] first clearly related the development of keratoses and skin cancer to long-term ingestion of arsenic as Fowler's solution. The second of his four patients[2] was Dr. James H. Whittemore, a 41-year-old resident physician at the Massachusetts General Hospital. From age 20 he had had psoriasis and had treated himself with large amounts of arsenic for long periods. "Corns" developed on his palms and soles at age 34. At age 40 his hands were amputated because of fungating growths. He died 18 months later with metastases in the axillary glands, lungs, kidneys, adrenals and ribs.

Clinical evidence that long-term ingestion of arsenic predisposes to skin and visceral cancer is also found in studies of populations whose drinking water has been contaminated with arsenic. For over 100 years the inhabitants of Reichenstein in Silesia drank arsenic-contaminated water. Gold ores containing arsenic were smelted in this area, and arsenic from the fumes and slag contaminated the brooks from which drinking water was drawn. In one of these brooks arsenic was found in a concentration of 1.22 mg/dl (12.2 ppm*). In many of these people "Reichenstein's disease" developed, with gastrointestinal symptoms, mouth ulcers, perforation of the nasal septum, paresthesias and, especially, melanosis and keratoses of fingers and hands, and skin tumours in a high incidence. Over half of the people in the area died from visceral cancer.[5] After 1928, when a new water supply was provided, the disease virtually disappeared.[6]

In the province of Cordoba in Argentina, where the well water has a high concentration of inorganic arsenic (0.28 to 0.45 mg/dl = 2.8 to 4.5 ppm), Ayerza's disease often develops after a person has drunk the polluted water for 5 or 6 years.[7] Keratoses and keratoderma appear on the palms and soles, and skin cancers, mainly on the trunk and limbs. Liver and kidney ailments, often fatal, develop.

Lest one think that exposure to arsenic does not occur today, we have outlined in Table I four examples from the last 15 years in North America.

A selected review of the world literature on skin and internal cancer caused by ingestion of inorganic arsenic is outlined in Table II. Although the data are selected, they do show that of 916 individuals exposed to trivalent arsenic a skin cancer developed in 642 (70.1%) and an internal cancer in 58 (6.3%).

Present study

Methods

Seven cases were selected for study from the files of the Ontario Cancer Foundation and from our private files. Supplemental material was obtained from the charts of the Ottawa Civic Hospital and from personal interviews with the patients. The criteria used for selection were known long-term ingestion of inorganic arsenic (Fowler's solution) and signs of chronic arsenic intoxication, specifically keratoses of the palms and soles (Fig. 1). The duration of exposure was calculated from the time when arsenic therapy was begun.

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*ppm = parts per million $\approx$ mg/l. Recommended Canadian standards for drinking water are: acceptable, 0.01 ppm; maximum permissible, 0.05 ppm; and emergency, 0.3 ppm.[4]

Findings (Table III)

All seven patients in the study, three women and four men, were 60 years or older. Two patients had died at the time of the review. Onset of arsenic treatment varied from childhood to young adulthood. In the four cases in which duration of treatment could be reliably determined the period varied from 17 to 25 years. In the other three cases, records allowed us to conclude confidently that therapy was of long duration (more than 5 years).

Table I—Examples of exposure to arsenic during last 15 years

Year and reference no.	Location	Source	Arsenic concentration (ppm*)	Disease and comments
1961[8]	Moira River basin, Madoc, Ont.	Smelting plant	Moira River 1971, 0.22 1972, 0.08 1973, 0.15 Moira Lake 1970, 0.09 1971-72, 0.05 1973, 0.04	None known.
1969[9]	Yellowknife, Northwest Territories	Gold mine smelter	Town water supply 1951-69 15% acceptable 70% below maximum permissible 15% above maximum permissible	Among 369 resident males, one basal cell carcinoma (type not stated). No mention of keratoses of palms or soles. High prevalence of chronic, nonspecific respiratory disease, neurologic abnormalities and electrocardiographic changes.
1973[10]	Perham, Minnesota	Well water	21 and 11.8 ppm	13 affected: mainly gastrointestinal complaints, acute and subacute intoxication.
1974[11]	Montréal	Kelp preparation	16 to 58 μg/g of product (16 to 58 ppm)	None.

*ppm = parts per million.

Table II—Selected review of reports of cancer due to ingestion of inorganic arsenic

Year and reference no.	Total no. of patients	Source of arsenic	No. with cancer		Comments
			Skin	Internal	
1947[6]	143	Medicine	143	13	116 had keratoses of palms and soles. Definitive review up to 1947.
1953[12]	18*	Mainly Fowler's solution	18	6	Internal cancers: esophagus, 1; bladder, 2; colon, 1; tonsil, 1; lung, 1. Some had more than one type of cancer.
1957[14]	27	Moselle vintner's "house drink" (0.2 to 8.9 mg/dl of As_2O_3, or 2 to 89 ppm)	5	15	Internal cancers: bronchial, 12; malignant mesenchymal tumours of liver, 3. Postmortem studies in all 27.
1958[15]	16	Pesticides used by vineyard workers	7	11	Internal cancers: bronchial, 9; bile duct, 1; malignant lymph node, 1.
1958[16]	2	Medicine(1) Potato spray (1)	1	2	Internal cancers: hemangioendothelioma of liver, 1; carcinoma of head of pancreas, 1.
1963[17]	10	Medicine	10	None listed	
1964[18]	1	Medicine	1	1	Larynx and tongue cancers.
1965[19]	262	Medicine	21	None listed	40% had keratoses of palms and soles and 8% had skin cancers, both related to dose of arsenic.
1967[20]	7	Pesticides used by vineyard workers	7	None listed	All had keratoses of palms and soles.
1968[21]	428	Well water (0.25 to 0.85 ppm)	428	9	Internal cancers: nasal fossa, 1; larynx, 1; bladder, 1; hepatomas, 4; "mediastinal" tumour, 1; rectal tumour. 1.
1968[22]	1	Medicine	0	1	Hemangioendothelial sarcoma of liver.
1969[23]	1	Medicine	1	0	
Total	916		642	58	

*A total of 27 patients, but 9 were previously reported[13] and are included in the total of reference 6.

Palmar and plantar keratoses occurred in all the patients a minimum of 15 years and a median of 24 years after onset of arsenic therapy. Other keratoses occurred in two of the seven patients, on either the torso or the face.

Classically, the keratoses occur especially on the palms and soles but may be found anywhere on the skin. The most characteristic form is punctate keratoses of the palms and soles, with numerous small, horny, corn-like elevations, usually 2 to 5 mm in diameter. They occur frequently as epidermal pegs that can be picked out of their keratotic beds. They are frequently on the thenar and lateral borders of the hand, at the roots or on the side surfaces of the fingers, and sometimes also on the back of the phalangeal joints. On the soles the sites of predilection are the heels and the anterior portion of the soles. The corns may be confluent, forming wart-like excrescences, but, unlike true warts, they do not have a papillary structure and do not push apart the skin lines. Sometimes only the palms or the soles are affected. Rarely there is a more diffuse keratosis of the palms and soles, giving the skin a leathery appearance (diffuse keratoderma). The punctate, horny thickenings may be on an erythematous base, or a horny patch may be surrounded by an erythematous halo. Rarely the punctate keratoses are combined with the keratoderma. The keratoses of palms and soles are usually symmetrically distributed. Fissures may occur on the keratoses.

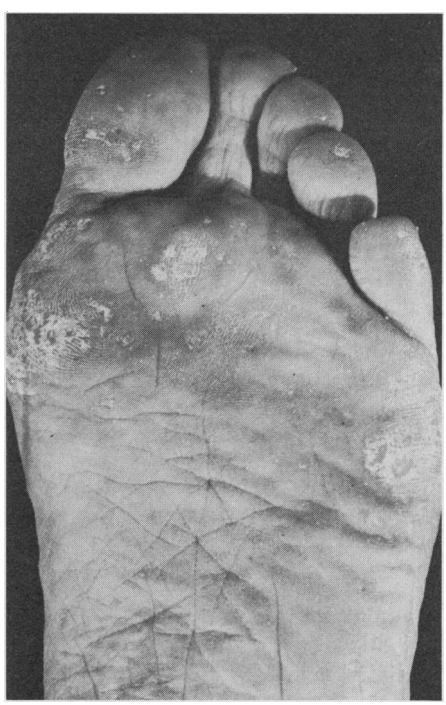

FIG. 1—Plantar keratoses (patient 5, present series).

The differential diagnosis of the punctate keratoses may include keratotic verrucae, multiple keratotic corns, keratotic psoriasis and other unusual types of keratosis punctata.

Basal cell carcinoma occurred in six of the seven patients a minimum of 15 years and a median of 43 years after onset of arsenic therapy. The superficial multicentric type of basal cell carcinoma occurred in all but patient 1. The lesions usually appeared on the torso but also occurred on the head and extremities. In five of the six patients the lesions were multiple; one patient had more than 50 tumours.

Carcinoma in situ developed in four of the seven patients a minimum of 39 years and a median of 44.5 years after onset of arsenic therapy. Lesions occurred on the chest, face, hand and leg. No patient had more than two lesions. Three patients had squamous cell carcinoma after a long period — 47, 50 and 51 years (median, 50 years). The sites of occurrence were the torso and the thigh. The number of lesions was recorded as few in one patient and only one in the other two patients.

Carcinoma other than of the skin occurred in two patients. In one an adenocarcinoma of the right breast developed 28 years after the onset of ingestion of arsenic and an adenocarcinoma of the left breast 11 years later. In the second patient a carcinoma of the colon developed 63 years after onset of arsenic therapy.

One of the patients died from a basal cell carcinoma of the face that eroded through the skull and caused death from local extension. The other patient died from a myocardial infarction.

Discussion

Frost[24] did not believe arsenic is a carcinogen. While undoubtedly all who ingest arsenic in either drinking water or wine do not develop skin cancer it is obvious that some do. Yeh, How and Lin[21] estimated that, among 40 421 inhabitants of 37 villages in Taiwan whose drinking water had a relatively high concentration of arsenic, 18.5% had skin manifestations of chronic arsenism (hyperpigmentation, keratoses or skin cancer).

Graham, Mazzanti and Helwig's[25] proposition that Bowen's disease in areas not exposed to sunlight is caused by arsenic ingestion has not been repeatedly shown to be true. Also, their patients did not regularly have palmar and plantar keratoses and superficial multicentric basal cell carcinomas on the torso — hallmarks of long-term ingestion of trivalent inorganic arsenic.

It is not easy to generalize on the type and location of cancers other than of the skin reported in patients who have been exposed to trivalent inorganic arsenic, but basically they are found in the respiratory tract (tongue, tonsil, nasal fossa, larynx, lung) and gastrointestinal tract (esophagus, colon) as well as the liver and pancreas. Bladder cancer has occasionally been reported.

There are many ways in which a person can be exposed to arsenic. It can be ingested in drinking water, food or medicine, inhaled as a component of dust in the air or absorbed through the skin by contact with arsenical dusts or solutions. Because small amounts of arsenic are present in the environment (Table IV) everyone is exposed. Arsenic has been reported in large amounts in cigarettes (42 mg per cigarette[25]) and presumably is in cigarette smoke.

Table IV—Common concentrations of arsenic in the environment[26]

Source	Concentration (ppm)
Ground water	0 — 55
Surface water	0 — 80
Sea water	0.001 — 0.08
Fish food	3 — 170
Plants	0.023 — 0.25
Soil	0.03 — 0.25
Wine	0.008 — 0.85
Urban air	<0.0000077 — 0.00049*

*< 0.01-0.63 μg/m³

Table III—Summary of cases of seven patients with signs of chronic arsenic intoxication and history of long-term ingestion of inorganic trivalent arsenic

Patient no.	Age (yr)	Sex	Treatment: Age at onset (yr)	Treatment: Duration (yr)	Development of cancer; no. of years after onset of arsenic therapy: Palmar and plantar keratoses	Basal cell carcinoma: Onset	Basal cell carcinoma: Type and no.	Carcinoma "in situ": Onset	Carcinoma "in situ": No.	Squamous cell carcinoma: Onset	Squamous cell carcinoma: No.	Carcinoma other than of skin	Other diseases	Cause of death
1	60+	F	Childhood	Unknown	15	15	Multiple superficial multicentric, one deeply invasive	—	None	50	Few	—	—	Basal cell carcinoma, local invasion, age 60
2	75+	M	Approx. 20	Unknown	Unknown	41	Few superficial multicentric	44	2	—	None	—	Arteriosclerotic heart disease, hypertension, hyperthyroidism	Myocardial infarction, age 75
3	60	F	20	20	22	19	50+ superficial multicentric	39	1	—	None	—	—	Alive
4	63	F	Approx. 7	Approx. 25	28	45	Multiple superficial multicentric	45	1	47	1	Right breast, 28; Left breast, 39		Alive
5	71	M	7	24	24	53	Multiple superficial multicentric	48	1	—	None	Colon, 63	Acute cholecystitis	Alive
6	63	M	25	17	25	—	—	—	None	—	None	0	Myocardial infarction	Alive
7	87	M	Young man	Unknown	Unknown	50	Multiple superficial multicentric	—	None	51	1	0	Arteriosclerotic heart disease	Alive

All forms of arsenic are not equally carcinogenic. Almost all reports indicate that the trivalent inorganic form is the real culprit. The pentavalent inorganic form only rarely is reported as causing cancer; it is assumed that there is some breakdown from the pentavalent to the trivalent form. The organic arsenical compounds, particularly the antisyphilitics such as arsphenamine (salvarsan), neoarsphenamine (neosalvarsan) and oxophenarsine hydrochloride (Mapharsen), are not carcinogenic because the arsenic ion is not readily available as a cellular toxin.[26]

One problem in establishing the carcinogenic activity of arsenic is that no animal models exist. Apparently arsenic does not affect animals in the same way as it does humans. Another problem is the difficulty in determining exact amounts of arsenic ingested in patients with evidence of chronic arsenic intoxication. Neubauer[6] and Fierz[19] tried to do this, and Fierz showed that the incidence of palmar and plantar keratoses and skin carcinoma increased with larger doses of the arsenical. There are no comparable figures for carcinomas of sites other than skin supposedly induced by arsenic.

The arsenic does not remain in the tissues for the total time required for the keratoses or skin cancers to develop; it certainly stays there for some years, but not the 10 to 15 or 20 years that often pass before the manifestation of lengthy arsenic exposure becomes obvious. Presumably some cellular change is induced by the arsenic and continues even in its absence. In our series the median time from commencing ingestion to onset of lesions was 24 years for palmar and plantar keratoses, 43 years for basal cell carcinoma, 44.5 years for carcinoma in situ and 50 years for squamous cell carcinoma. By the time neoplasms have developed, the concentrations of arsenic in the skin, hair and nails may have returned to normal and it is impossible to prevent more lesions developing by removing residual traces of arsenic by treatment with dimercaprol (BAL).[27]

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Postgraduate Courses

SYMPOSIUM — LES ULCÈRES GASTRODUODÉNAUX. Université Laval. Les 21-22 novembre 1975. Renseignements: Dr Robert Gourdeau, Faculté de médecine, Université Laval, Québec, Qué. K1K 7P4

CREATIVE SEXUALITY. Hotel Toronto. Nov. 26 to 28, 1975. Seminar with Drs. Noam and Beryl Chernick. Information: Creative Sexuality, Ste. 400, 73 Richmond St., Toronto, Ont. M5H 2A1