Arsenic-Induced Skin Lesions among Atacameño People in Northern Chile Despite Good Nutrition and Centuries of Exposure

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It has been suggested that the indigenous Atacameño people in Northern Chile might be protected from the health effects of arsenic in drinking water because of many centuries of exposure. Here we report on the first intensive investigation of arsenic-induced skin lesions in this population. We selected 11 families (44 participants) from the village of Chiu Chiu, which is supplied with water containing between 750 and 800 µg/L inorganic arsenic. For comparison, 8 families (31 participants) were also selected from a village where the water contains approximately 10 µg/L inorganic arsenic. After being transported to the nearest city for blind assessment, participants were examined by four physicians with experience in studying arsenic-induced lesions. Four of the six men from the exposed village, who had been drinking the contaminated water for more than 20 years, were diagnosed with skin lesions due to arsenic, but none of the women had definite lesions. A 13-year-old girl had definite skin pigmentation changes due to arsenic, and a 19-year-old boy had both pigmentation changes and keratoses on the palms of his hands and the soles of his feet. Family interviews identified a wide range of fruits and vegetables consumed daily by the affected participants, as well as the weekly intake of red meat and chicken. However, the prevalence of skin lesions among men and children in the small population studied was similar to that reported with corresponding arsenic drinking water concentrations in both Taiwan and West Bengal, India—populations in which extensive malnutrition has been thought to increase susceptibility. *Key words*: arsenic, Chile, drinking water, nutrition, skin lesions. *Environ Health Perspect* 108:617–620 (2000). [Online 26 May 2000]
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Chronic ingestion of inorganic arsenic causes characteristic skin lesions including pigmentation changes, mainly on the trunk and extremities, and keratoses of the palms of the hands and soles of the feet. Hyperpigmentation has been described as raindrop-shaped discoloration spots, diffuse dark brown spots, or diffuse darkening of the skin on the limbs and trunk. Simple keratoses usually appear as bilateral thickening of the palms and soles; nodular keratoses appear as small protrusions usually confined to the palms and soles (*1*). Skin lesions due to arsenic ingestion are a problem in themselves, and there is some evidence that those who have them may be at particularly increased risk of arsenic-caused internal cancers (*2*). Large numbers of affected patients have been reported in arsenic-endemic regions of various countries including Argentina (*3,4*), Taiwan (*5,6*), Bangladesh (*7,8*), and West Bengal, India (*1,9*). Cases of arsenic-induced skin lesions were also reported in the major northern city of Antofagasta in Region II of Chile, where high concentrations of arsenic (approximately 800 µg/L) were present in water sources until the 1970s, when a treatment plant was installed to remove arsenic (*10,11*). Subsequently, a treatment plant was also installed in Calama, the second largest city in Region II.

The installation of these treatment plants, the first large-scale arsenic removal plants in the world, dramatically reduced the number of those exposed to high levels of inorganic arsenic in northern Chile. However, pockets of continued exposure remain. The best known and largest of these exposed areas is the village of San Pedro de Atacama, where sectors of inhabitants drink water containing approximately 600 µg/L arsenic. It has been thought that this population does not have a high incidence of arsenic-related diseases (*12,13*). This belief led to the intriguing theory that the local people were resistant to arsenic-caused health effects. Archeologic evidence indicates that the Atacameño people have lived in the region for over 9,000 years (*14*), and the only drinking water sources in this extremely dry desert region are rivers originating from springs in the Andes Mountains, many of which contain high levels of inorganic arsenic. It was postulated that as a result of many centuries of exposure (*12,15*) the population might have developed some resistance to the toxic effects of arsenic.

Another hypothesis for the perceived reduced effects of arsenic can be based on the absence of severe malnutrition in the Atacameño people. Evidence in some populations studied has suggested that arsenic-induced health effects are associated with malnutrition (*16–20*). Thus, both inherited resistance and/or good nutrition might explain the apparent reduced effects of arsenic in this population.

One potential biologic mechanism for a reduced response to inorganic arsenic is enhanced metabolism involving methylation of inorganic arsenic to less toxic forms. However, a study we conducted in San Pedro de Atacama demonstrated that arsenic metabolism as assessed by methylation patterns in urine was similar in the Atacameños as compared to that in other populations, both during exposure and after exposure was reduced (*12,21*). In addition, there was evidence that arsenic ingestion by these same people was causing an increase in the number of bladder cells with micronuclei (*22–24*), a biologic marker postulated to be related to increased risks of bladder cancer (*25*). The possibility that there were reduced arsenic skin effects in the Atacameño people, and the apparent absence of a biologic mechanism based on arsenic metabolism, were of potential scientific and public health importance. However, the evidence for reduced arsenic skin effects in this population was largely anecdotal.

In 1998, we became aware of a small village called Chiu Chiu in the region [population 247 (*26*); elevation 8,000 ft; average rainfall approximately 1 inch/year; the main economic activity is growing fruits and vegetables]. Drinking water containing 750–800 µg/L arsenic was piped to homes in Chiu Chiu. Our most recent measurements from

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We thank the participants, in particular the families from the control village, who left their homes at 0700 and returned at 1900 to help their "hermanos" in Chiu Chiu.

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three different water sources in Chiu Chiu were 735, 762, and 763 µg/L arsenic. A sample obtained in 1992 reportedly contained 772 µg/L (*26*). In fact, the Chiu Chiu water source was the pipe that delivered untreated water a little over 400 km for arsenic removal and subsequent use in the city water supply of Antofagasta. The residents of Chiu Chiu are predominantly Atacameño and seem to have good nutrition. Many residents work outside the village and use other water sources, but our preliminary investigations indicated that we would be able to find approximately 10 families who had lived there for 10–20 years or more and who predominately used the village water supply for drinking. We invited resident families who had been there the longest and whose main source of drinking water was from the village supply to participate in an epidemiologic study focusing on skin lesions. The nearest village with low-arsenic water was Caspana, 70 km away [population 274 (*26*); elevation 11,000 ft; average rainfall approximately 1 inch/year; the main economic activity is growing fruits and vegetables]. The arsenic concentration was 12.7 µg/L in a sample we recently analyzed; it was 9 µg/L in 1992 (*26*). Eight families from this control village participated in the investigation. The fundamental objective for the selection of a control village was to ensure that the examining physicians were blind to exposure.

Materials and Methods

The study was a blinded cross-sectional survey of families from the two villages conducted over a 4-day period. The objective was to find the 10 most exposed families living in Chiu Chiu. We used four selection criteria. First, we selected families that included at least one adult male, one adult female, and two children older than 5 years of age. Second, we selected families in which the two adults had lived in Chiu Chiu for at least 10 years. Our initial search was to find families in which both adults had lived and worked in Chiu Chiu for at least 20 years, but after extensive searching revealed that we had exhausted all such families, we began admitting families in which one adult had 20 years of residence and the other had at least 10 years. Third, we selected families whose children had been born in Chiu Chiu and who had resided there since birth. Fourth, we selected families whose principal source of water was the village supply. The objective from the unexposed village was also to find 10 families, each with at least two children. We chose families in which both parents had lived in Caspana for many years and had never lived or worked in a village that had arsenic in the drinking water. When a family selected in either Chiu Chiu or Caspana had more than two children, the children closest to 10–12 years of age were invited to participate in the study.

Meetings took place with the mayor and prominent residents of each village to discuss the project and identify families that met the inclusion criteria. The study was explained to potential participants in each village at open community meetings and by local residents recruited to assist with the study. In villages with populations as small as these, residents who have lived there for any length of time are well known to all of the other village members.

The families who agreed to participate were brought by bus from their villages to the public health clinic in the city of Calama (35 km from Chiu Chiu and 80 km from Caspana), where they were interviewed and examined after giving informed consent. The families were then taken home by bus at the end of each day. When needed, home care was arranged for nonparticipating children, and replacements were paid to conduct work normally done by the adults. Meals were provided to participants throughout the day. The study included a general medical examination for each participant; findings were reported to each family on the same day.

Each family member was given a thorough skin examination by four physicians working separately. One physician was involved with inviting families to participate, and was therefore not fully blind to village of residence at the time of physical examinations. The other three physicians were blind to the village of residence of each subject, as well as to duration of exposure if they were from Chiu Chiu. The first physician was a practicing dermatologist who has examined numerous patients with arsenic-induced skin lesions in Chile; the second has evaluated many thousands of patients with arsenic-induced lesions in West Bengal, India; and the third has been involved with arsenic investigations in the United States and elsewhere, and recently authored a clinical guidance document for the evaluation of patients with potential exposure to arsenic in drinking water (*27*). Before commencing the study, the examining physicians studied and discussed slides of arsenic-caused skin lesions from previous investigations to reduce variation in how they would classify them.

Each physician separately examined each participant and entered findings on a two-page structured report. One page was devoted to nodular and/or diffuse keratoses of the palms of the hands and the soles of the feet. The second page was devoted to pigmentation changes on the chest, back, arms, and elsewhere. All observations were classified as definitely, probably, possibly, or not related to arsenic. Forms were then collected and assessed by the study director. When two or more physicians indicated that arsenic-induced lesions were definitely, probably, or possibly present, the participant was reexamined by all four physicians together and a consensus diagnosis was made. In the consensus reexamination, each physician could enter revisions on his examination form without deleting or altering the original observations. A diagnosis of arsenic-induced skin lesions was made if at least one of the four examining physicians indicated that one or more skin findings were definitely of a type caused by arsenic and a further two of the examining physicians categorized them as at least probably related to arsenic. However, the findings presented in this report are based on the original individual observations of the physicians and were not affected by revisions made during the joint examinations.

In addition to the physical examination, each family was also given a detailed structured interview lasting approximately 1 hr. The questionnaire covered place of birth, ethnicity, residences, lifetime drinking water sources, and dietary habits. Family members were asked about current and past water consumption as water, coffee, tea, water added to powdered milk, water added to concentrated juices, and water in soups. The time available for the interview did not allow for an extensive dietary questionnaire. Diet was included in an abbreviated fashion to highlight any major nutritional deficiencies or excesses that may have occurred on a family level. We collected information on family fruit, vegetable, and meat consumption per week. We measured the height and weight of each participant.

Results

A total of 11 families participated from Chiu Chiu, each consisting of two adults and two children. No families that met the selection criteria refused to participate in the study. Subsequent to the study, an additional 19-year-old boy from Chiu Chiu was examined at the request of the participating parents; he is included in the enumeration of participants in Table 1. Eight families from Caspana participated, one of which had only one child. The age and sex distribution of participants is summarized in Table 1. The participants from Caspana were older than those from Chiu Chiu. Seventy-two percent of the participants from Chiu Chiu and all of the participants from Caspana reported their ethnicity as Atacameño. The remaining subjects from Chiu Chiu were members of other Chilean indigenous groups.

The presence of arsenic-related skin lesions is presented in Table 2 by duration of exposure to arsenic-contaminated drinking water. Four men from Chiu Chiu were diagnosed as having arsenic-induced skin lesions. Each of these men was Atacameño, two were current smokers, and two were former smokers. The average body mass index for these four men was 25.3 kg/m^2 [the U.S. average for adults older than 20 years of age is 25.5 kg/m^2 (*28*)]. The two men who had lived in Chiu Chiu for more than 40 years both had arsenic-related skin lesions. All four had pigmentation changes and two had keratoses. One of the four men had possible keratoses. One man had signs of Bowen disease, the skin cancer classically related to arsenic ingestion. Of the four men who had lived in Chiu Chiu for 20–40 years, two were diagnosed with skin lesions caused by arsenic. The overall prevalence in those with more than 20 years of residence was therefore 4 of 6 (67%; 95% confidence interval, 22–96%). Detailed estimates of dose are under way, including urine analysis, but the preliminary estimates based on interview alone reveal that the affected men were drinking between 2 and 5 L arsenic-contaminated water per day.

Table 2 also shows that there were no women diagnosed with arsenic-induced skin lesions, even though eight had lived there more than 20 years. Some had possible skin changes due to arsenic, but the criteria necessary for diagnosis were not fulfilled in any instance.

Table 3 presents overall findings among Chiu Chiu children, all of whom had lived their entire lives in that village. One girl, 13 years of age, was diagnosed by all four examiners as having arsenic-related pigmentation changes. Two of the three blinded examiners stated that arsenic-related lesions were definitely present, and the third recorded that they were probable. During the formal study period no boys were diagnosed with skin lesions; however, the parents of the 13-year-old girl later asked us to examine her older brother, who was 19 years of age. All four of the physicians examined him (not blinded) and all agreed that he had definite keratoses on the palms of the hands and soles of the feet and definite pigmentation changes related to arsenic on his chest and back. This boy is included in Tables 1 and 3 along with other study participants.

Table 1. Average ages and sex distribution of study participants.

Village	Men	Women	Boys	Girls
Chiu Chiu				
No.	11	11	14	9
Average age	38	36	11	11
Age range	30–50	26–47	9–14	6–19
Caspana				
No.	8	8	6	9
Average age	48	46	13	15
Age range	29–67	35–64	7–18	10–19

Ages given in years.

All study participants appeared to be well nourished. Table 4 presents information related to nutritional status at the time of interview of the four affected men, who were all of average height and weight. Chiu Chiu is a vegetable- and fruit-growing village that specializes in carrots. Family interviews revealed that each family ate between 2 and 6 types of fruit each week (the most common were apples and oranges when in season) and between 7 and 11 types of vegetables (the most common were carrots, potatoes, and green beans; each of the four affected families consumed carrots every day of the week). Each of the affected families consumed both chicken and red meat at least once a week. The two affected children also appeared to be well nourished and were from the family of case 4.

Only one person in Caspana was diagnosed with arsenic skin lesions. Surprisingly, he had lived his entire life in Caspana and had no history of ever having consumed arsenic-contaminated drinking water. Two of the examining physicians concluded that he had definite skin pigmentation changes related to arsenic, and the other two diagnosed them as probable. Extensive questioning failed to reveal a source of exposure. However, he had regularly taken herds of llama and sheep out of Caspana for extended periods of time, a fact that raises the possibility that he may have consumed arsenic-contaminated water from springs in the mountains. We collected water samples from other springs and rivers in the area and are currently analyzing them for their arsenic content.

Discussion

This small but carefully designed study produced clear evidence that Atacameño men with good nutrition develop arsenic-induced skin lesions after prolonged exposure to arsenic in drinking water, despite the fact that their ancestors have had potential exposure to arsenic for thousands of years in the Andes mountains of northern Chile. This is the first study of arsenic-induced lesions in which potential diagnostic bias was avoided by having participants examined blind to exposure, village of residence, and water supply.

Four of six men with more than 20 years of exposure showed typical skin effects. This prevalence of effects can be compared to that reported in studies in Taiwan (*5,29*) and India (*1*). In the arsenic-endemic area of Taiwan, the overall prevalence of hyperpigmentation and keratoses is 18.3 and 7.1%, respectively (*5*), but the methods of selection of study subjects and age distributions were not given. Although detailed age-specific prevalence data for Taiwan are not available for comparison with the present study, they are available from a study in India. In a major population survey in West Bengal, among those whose drinking water contained > 800 µg/L arsenic, 6 of 55 men (11%) aged 30–59 had arsenic-related pigmentation changes of the skin (*1*). This prevalence in men in West Bengal is actually lower than that among men in Chiu Chiu in the present study (4 of 11, or 36% with pigmentation changes) despite the fact that the water in Chiu Chiu contained 750–800 µg/L arsenic. However, in West Bengal, 4 of 36 women (11%) aged 30–59 who were drinking water containing > 800 µg/L had pigmentation changes, whereas there were no definite cases in the present study. Nevertheless, finding just one woman with effects in the 11 exposed women would have led to the same prevalence estimate as in India, making it impossible to infer lower risks among women in Chile.

The prevalence of children younger than 20 years of age in West Bengal with skin pigmentation changes was 3 in 52 (6%) for girls and 2 in 57 (4%) for boys. The corresponding numbers in the present study are 1 in 9 (11%) for girls and 1 in 14 (7%) for boys. Little can be inferred from these small numbers, but the findings are consistent with risks in Chiu Chiu being similar to those found among highly exposed children in West Bengal.

The reason that clear cases of arsenic-related skin lesions among women were not found remains unknown. Although it is in part related to lower water consumption, other studies also indicate that women are less susceptible to arsenic-induced skin lesions than men, even with dose per body weight taken into account (*1*).

The limited nutritional data presented here provide no evidence of malnutrition. In fact, the local population of Chiu Chiu is famous for its cultivation of carrots and other vegetables. Each of the families with arsenic-induced skin changes consumed

Table 2. Chiu Chiu participants by duration of exposure and numbers affected with arsenic-related skin lesions.

	Exposure duration (years)		
	0–19	20–39	40+
Men (*n*)	5	4	2
With skin effects	0	2	2
Women (*n*)	3	5	3
With skin effects	0	0	0

Table 3. Chiu Chiu children by age (equals duration of exposure) with arsenic-related skin effects.

	Age (years)		
	0–9	10–14	15–19
Boys (*n*)	5	8	2
With skin effects	0	0	1
Girls (*n*)	1	7	–
With skin effects	0	1	–

Table 4. Weight, height, and nutritional information for the four affected men.

Case	Age (years)	BMI[d] (kg/m²)	Fruits[a] Servings/week	Fruits[a] Varieties	Vegetables[b] Servings/week	Vegetables[b] Varieties	Meats[c] Servings/week	Meats[c] Varieties
1	50	22.1	11	4	34	7	3	2
2	36	27.0	6	2	11	9	7	2
3	37	26.3	8	6	34	11	5	4
4	43	25.8	12	4	24	9	4	4

[a]Apples, pears, oranges, bananas, grapes, melon, quince, and pomegranate. [b]Carrots, potatoes, green beans, corn, peas, squash, lettuce, tomatoes, cabbage, peppers, and beterraga. [c]Chicken, beef, pork, llama, and fish. [d]The U.S. average body mass index (BMI) for men > 20 years of age is 25.5 kg/m² (*28*).

many vegetables, including carrots, every day. In view of the known conversion of some carotene to vitamin A in the body, it is apparent that high carotene intake and sufficient vitamin A do not prevent arsenic-induced skin lesions.

Archeologic evidence shows that the Atacameño people have inhabited these regions in the Andes mountains for approximately 9,000 years (*14*). It is reasonable to believe that the natural contamination of much of the water in the region has been present throughout this time. High concentrations of arsenic have been found in various tissues of mummified bodies in archeologic sites in the region dating as far back as 830 B.C. (*30*). Whereas little is known about the human reproductive effects of arsenic, it is reasonable to postulate that resistance to arsenic health effects might result in selective advantage, leading to the emergence of resistance in exposed populations (*15*). Also, an indirect mechanism for selective advantage has been proposed involving arsenic exposure contributing resistance to Chagas disease, which is endemic in this region. Chagas disease results in reproductive effects including congenital abnormalities, spontaneous abortion, and stillbirths (*12,31*). According to this theory, adaptation to high intakes of arsenic leads to the emergence of resistance to Chagas disease in Region II of Chile. However, the stimulus for the development of these theories was the presumed low incidence of arsenic-induced skin lesions in the Atacameño people (*32*). Based on the present study, the prevalence, if not the severity, of skin lesions among Atacameño people exposed to arsenic in drinking water may be as high as in the various populations in the world where the use of arsenic-contaminated drinking water commenced in recent years.

In conclusion, this study provides clear evidence that arsenic-induced lesions occur despite thousands of years of potential arsenic exposure to ancestors, and despite good nutritional status. High priority should be given to implementing plans to provide low arsenic water to this population. During the final revisions of this manuscript we were pleased to learn that the people of Chiu Chiu are now being provided water from Calama (45 µg/L arsenic) as an interim solution, and that the long-term solution will be the construction of a water treatment plant for this community.

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