Environmental Health Perspectives
Vol. 19, pp. 109–119, 1977

Effects and Dose–Response Relationships of Skin Cancer and Blackfoot Disease with Arsenic

by Wen-Ping Tseng*

In a limited area on the southwest coast of Taiwan, where artesian well water with a high concentration of arsenic has been used for more than 60 years, a high prevalence of chronic arsenicism has been observed in recent years. The total population of this "endemic" area is approximately 100,000. A general survey of 40,421 inhabitants and follow-up of 1,108 patients with blackfoot disease were made. Blackfoot disease, so-termed locally, is a peripheral vascular disorder resulting in gangrene of the extremities, especially the feet. The overall prevalence rates for skin cancer was 10.6 per 1000, and for blackfoot disease 8.9 per 1000. Generally speaking, the prevalence increased steadily with age in both diseases. The prevalence rates for skin cancer and blackfoot disease increased with the arsenic content of well water, i.e., the higher the arsenic content, the more patients with skin cancer and blackfoot disease. A dose–response relationship between blackfoot disease and the duration of water intake was also noted. Furthermore, the degree of permanent impairment of function in the patient was directly related to duration of intake of arsenical water and to duration of such intake at the time of onset. The most common cause of death in the patients with skin cancer and blackfoot disease was carcinoma of various sites. The 5-year survival rate after the onset of blackfoot disease was 76.3%; the 10-year survival rate was 63.3% and 15-year survival rate, 52.2%. The 50% survival point was 16 years after onset of the disease.

In a limited area on the southwest coast of Taiwan where artesian well water with a high concentration of arsenic has been used for more than 60 years, a high prevalence of chronic arsenicism has been observed in recent years (*1–3*). It is well known that hyperpigmentation, keratosis, and cancer are the major manifestations of chronic arsenicism from any source (*4*), but peripheral circulatory disorders have also been reported occasionally in chronic arsenicism (*5–9*). It seems reasonable to assume that arsenic may be the common etiological factor for skin cancer and blackfoot disease. A positive association between the arsenic level of drinking water and the prevalence of skin cancer in endemic areas of chronic arsenicism has been reported from the district of Reichenstein, Silesia, Poland (*7*), Cordoba Province, Argentina (*10*), and most recently from Antofagasta, Chile (*11*). Although reliable information about the number of cases of arsenical cancer of the skin is Reichenstein is not available, Arguello and Tello identified a total of 148 cases in Cordoba Province (*12*). There were no statistical studies in either population group.

Regarding peripheral circulatory disorders, at least 15 cases of chronic arsenicism have been reported with gangrene of the extremities (*5, 7, 8, 13–19*). Although detailed pathologic observations on autopsy specimens or amputated limbs are lacking in the cases reported, the gangrene appears to result from arteriosclerosis and thromboangiitis obliterans (*5*).

After a preliminary survey of the endemic area in Taiwan, we have learned that a high percentage of the inhabitants suffered from chronic arsenicism, and a considerable number had arsenical skin cancer or blackfoot disease, a folk term for a peripheral vascular disorder resulting in gangrene of extremities, especially the feet (*1–3*). The affected area afforded us a unique opportunity to study systematically the epidemiologic, clinical, and pathologic aspects of both these diseases (Figs. 1 and 2).

*Department of Medicine, National Taiwan University, College of Medicine, Taipei, Taiwan, Republic of China.

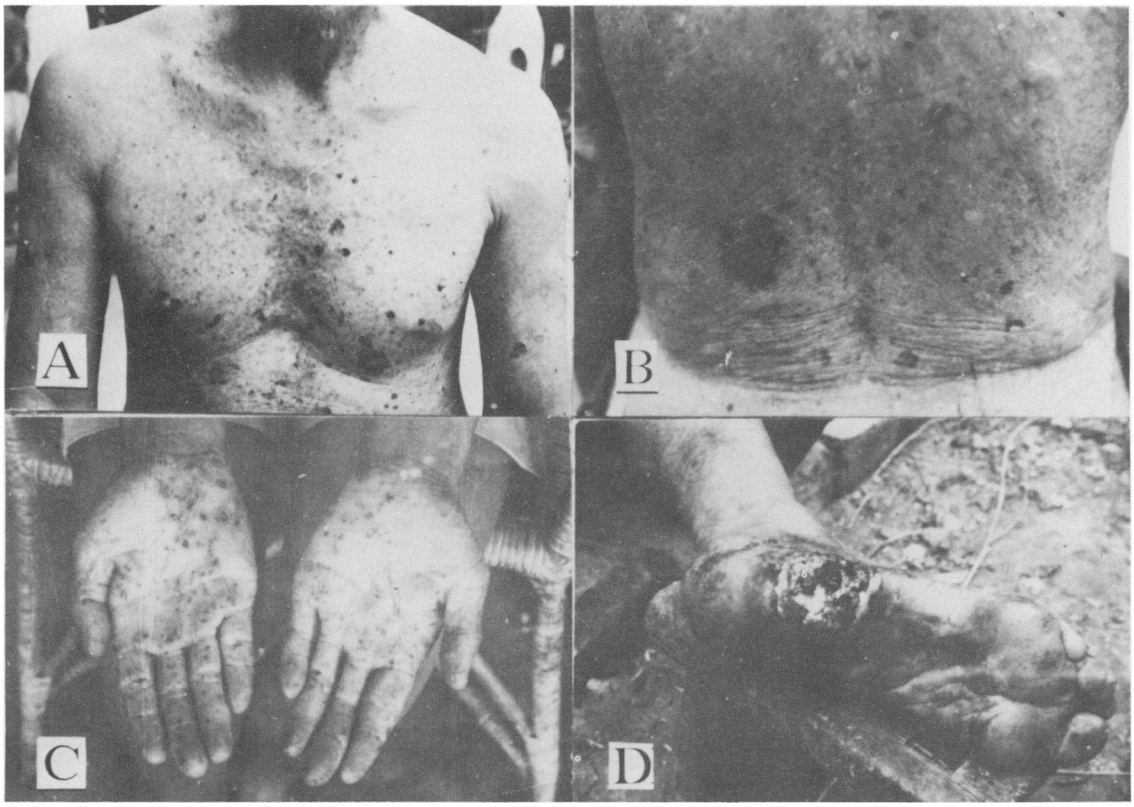

FIGURE 1. Skin manifestations: *(A)* typical arsenical hyperpigmentation of skin in a 54 yr old male; *(B)* hyperpigmentation with Bowen's disease on the back in a 60 yr old male; *(C)* arsenical keratosis in a 39 year old male. (note numerous nodular and papular keratotic lesions on palm and lateral surfaces of fingers); *(D)* large dirty, fungating tumor mass developed on the right sole in a 59 yr old male; biopsy revealed an epidermoid carcinoma.

Materials and Methods

Population of the Endemic Area

We use the term "endemic" area to refer to the total region where artesian wells providing water with a high concentration of arsenic have been used for a long time or are still used, and where a high percentage of inhabitants suffer from skin lesions associated with chronic arsenicism, i.e., hyperpigmentation, keratosis, and cancer. The total endemic area thus defined consists of two districts (Peimen and Yi-Chu), three towns (Putai, Hsueh-Chia, and Yen-Hsui), and three villages (two from the suburb of Tainan City and one from the An-Ting district). Census records obtained from villages in the endemic area showed that the entire population at risk is 103,154 (51,289 males and 51,865 females), although approximately 10% of the people are constantly away from home, either for employment or for other reasons. The inhabitants are mostly engaged in farming, fishing, or salt production. The socioeconomic state of the people is poor. As is usually true in rural areas in southern Taiwan, the people subsist on food low in protein and fat; carbohydrate, rice, and sweet potatoes constitute the main part of their diet. The customs and habits of the inhabitants do not differ from those in other parts of Taiwan.

Artesian Wells

Artesian wells have been in use since the decade 1900–1910. In most parts of the area where artesian wells are still in use, they are 100 to 280 m deep, 80% being between 120 and 180 m in depth. In 1956 water was piped to many places mostly from the reservoir of the Chia-Nan irrigation system, this water having an arsenic content of 0.01 ppm. In 1966 a tap water supply was made available to the majority of the endemic area in Tainan County. There will be no more use of artesian wells in the study area. In the villages surveyed, the arsenic content of the well water ranged from 0.01 to 1.82 ppm, including four shallow wells (*20*). The water from the artesian wells was not always as high in arsenic content, for

FIGURE 2. Gangrene of extremities: *(A)* gangrene of right foot and spontaneous amputation of left toes in a 17 yr old male; *(B)* gangrene of left foot in a 62 yr old male; *(C)* loss of first and second toes of right foot, and ulcer on left big toe in a 54 yr old male; *(D)* gangrene of left second and third fingers in a 53 yr old female.

some from the neighborhood of the endemic area had an arsenic content of only 0.01 ppm. Shallow wells were usually almost free from arsenic (0.001 ppm).

Methods of Survey

By the end of 1965 a general survey of the entire population of 40,421 in the endemic area had been completed. Ten of the 37 villages are in Chai-yi County, 25 in Tainan County, and 2 in a suburb of Tainan City.

The survey was house-to-house and every member of the family was examined. Particular attention was paid to skin lesions, i.e., the pigmentation of unexposed body surfaces, keratoses (especially on palms and soles), and cancers. In addition, the blood pressure of persons over age 20 was taken; pulsation of the dorsalis pedis and posterior tibial arteries was noted; evidence of any peripheral vascular disorder was recorded. The clinical examinations were done by two young doctors assisted by a nurse and clerk, and all lesions they found were checked by one or two of the experienced senior members of our staff. A total of 303 arsenical skin cancers in 184 patients were studied histologically. These lesions are discussed in detail elsewhere (*21*). From the villages surveyed, we examined 142 water samples from 114 wells, of which all but four were artesian (Fig. 4). The villages in

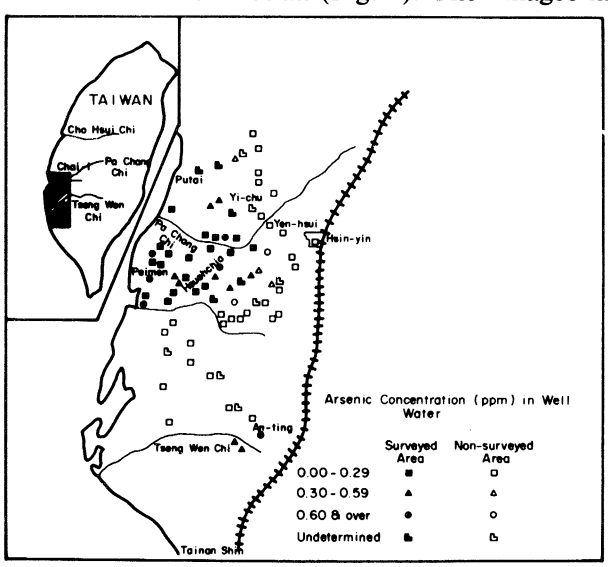

FIGURE 3. Area of endemic chronic arsenic poisoning on Taiwan.

the endemic area that still used artesian wells at the time of examination and had water with an arsenic content over 0.01 ppm are shown in Figure 3. The method used for determination of the arsenic content of the water was that of Natelson (*22*).

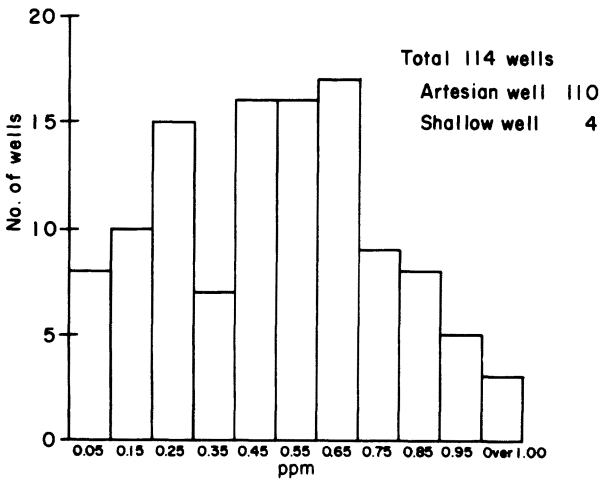

FIGURE 4. Concentrations of arsenic (ppm) in well water of surveyed villages.

Method of Follow-Up Study of Blackfoot Disease

A total of 1108 patients with blackfoot disease in the entire endemic area were examined by the author himself during 1958 and 1975. There 669 males and 439 females. Each patient was carefully studied. Criteria for diagnosis depend upon (1) objective signs of ischemia, i.e., absence or diminution of arterial pulsations, pallor on elevation or rubor on dependency of ischemic extremities, and various degrees of ischemic changes in the skin and (2) subjective symptoms of ischemia, i.e., intermittent claudication, pain at rest, and ischemic neuropathy. Follow-up was attempted by a variety of methods, including direct follow-up physical examination, several mailings to patients, and search of death certificate files. By the end of the follow-up period 528 patients had died, giving an overall fatality rate of 47.7%. A history of typical ischemic symptoms such as numbness or intermittent claudication antecedent to the ulcer or gangrene has been used in estimating the date of the onset of blackfoot disease. The duration of intake of arsenical water at the time of onset represents the period of time between first use of such intake and the time of onset of the disease. Duration of intake of arsenical water represents the duration of time during which the patient started drinking artesian well water up to the time of survey or up to the time of change of source of drinking water. For native patients the duration is estimated to be equivalent to their ages, but for the patients who came from areas without artesian wells the duration was counted as starting from the year of their arrival.

Evaluation or rating of permanent disability has long been recognized as an important and complex subject. The percentage of permanent impairment due to amputation has been taken from the literature (*23*).

Permanent impairment of the back and extremities is divided into five classes, from the minimal nonimpairing (class 1) to the most severely impairing (class 5). Percentage values representing the impairment of the patient as a whole man were classified as follows; class 1, nonimpairing, 0% impairment; class 2, mild impairing, 5–24% impairment; class 3, moderate impairing, 25–49% impairment; class 4, moderately severe impairing, 50–74% impairment; class 5, most severely impairing, 75–90% impairment.

The original classification did not have 1–4% of the impairment of the whole man, but many minor amputations occur in mild cases of Blackfoot disease. For this reason an additional class intermediate between 1 and 2 was added to represent very mild impairment, 1–4% of impairment.

Results

Age-Specific and Sex-Specific Prevalence of Skin Cancer

Of the population of 40,421,428 (10.6/1000) had arsenical skin cancer (Table 1). There were no patients under 20 years of age. The prevalence rate increased markedly with age, except for females above age 70. Over 10% of the people above age 60 were affected by skin cancer. The overall male-to-female ratio was 2.9 to 1, with males having a higher rate in all age groups above 30 years.

Table 1. Age-specific and sex-specific prevalence rate for skin cancer.

	Male		Female		Total	
Age	Per 1000	Number	Per 1000	Number	Per 1000	Number
0-19	—	0	—	0	—	0
20-29	1.0	2	1.1	3	1.1	5
30-39	9.7	20	1.5	4	5.0	24
40-49	25.9	40	8.0	16	15.7	56
50-59	80.8	99	28.9	38	53.7	137
60-69	124.8	92	57.0	40	91.9	132
70+	209.6	57	53.8	17	125.6	74
Total	16.1	310	5.6	118	10.6	428

Prevalence of Skin Cancer with Varying Arsenic Concentration in Well Water

The villages surveyed were arbitrarily divided into three groups, according to the arsenic concentration in the well water being designated "low" (below 0.3 ppm), "mid" (0.3–0.6 ppm), and "high" (above 0.6 ppm) groups. A clear-cut ascending gradient of prevalence of skin cancer from low (L) to mid (M) to high (H) groups was found for both sexes in the three age groups: e.g., 20–39 yr (H 11.5, M 2.2, L 1.3): 40–59 yr (H 72.0, M 32.6, L 4.9): 60 years and over (H 192.0, M 106.2, L 27.1), as shown in Figure 5. Another group, "undetermined," included those villages where either artesian wells with arsenic-polluted water were no longer in use, or the difference in the arsenic content in water from various artesian wells in the same village was so great that it was impossible to put them into any of the above-mentioned classifications. The prevalence rate of the "undetermined" group was similar to that of the "mid" group.

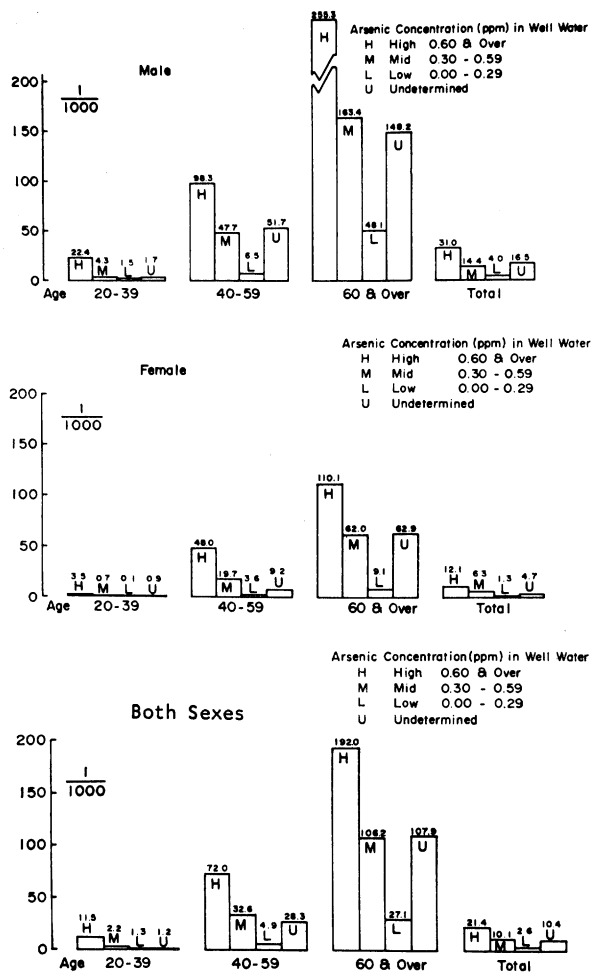

FIGURE 5. Age-specific and sex-specific prevalence rate per 1000 for skin cancer by arsenic concentration in well water.

Age-Specific and Sex-Specific Prevalence of Blackfoot Disease

The overall prevalence was 0.9–1.1% for males and 0.7% for females (Table 2). After age 40, the rates for males were significantly higher than for females. The prevalence rose steadily until age 70 for both sexes; after that, rates decreased. The overall male-to-female ratio was 1.3 to 1.

Table 2. Age-specific and sex-specific prevalence rate for blackfoot disease.

	Male		Female		Total	
Age	Per 1000	Number	Per 1000	Number	Per 1000	Number
0-9	0.3	2	—	0	0.1	2
10-19	1.2	5	1.4	6	1.3	11
20-29	12.1	22	6.5	18	8.7	40
30-39	12.7	26	10.8	30	11.6	56
40-49	30.0	46	19.6	40	24.0	86
50-59	40.6	52	33.9	47	37.1	99
60-69	68.2	52	15.2	11	42.3	63
70+	23.0	7	15.8	6	19.0	13
Total	10.7	212	7.3	158	9.0	370

Prevalence of Blackfoot Disease with Varying Arsenic Concentration in Well Water

According to the same above-mentioned classification (low, mid and high groups) in the villages surveyed, the prevalence rate for blackfoot disease also revealed a clear-cut ascending gradient from low to mid to high groups for both sexes in the three age groups: e.g., 20–39 yr (H 14.2, M 13.2, L 4.5): 40–59 yr (H 46.9, M 32.0, L 10.5); 60 yr and over (H 61.4, M 32.2, L 20.3), as shown in Figure 6. The greater the arsenic content, the higher the prevalence of blackfoot disease.

Combination of Skin Cancer and Blackfoot Disease

In our survey of chronic arsenicism in a population of 40,421 in 37 villages, we found 428 cases of skin cancer and 370 cases of blackfoot disease giving an observed rate per 1000 of 10.59 and 8.96, respectively. The combination of skin cancer and blackfoot disease occurs in 61 cases, or 1.51 per 1000, whereas 4 cases, or 0.09 per 1000, are expected. Thus the ratio of observed to the expected is 16.77. This ratio indicates that the coincidence of the two conditions cannot be attributed to chance, and incriminates a common or underlying factor, namely, chronic arsenicism.

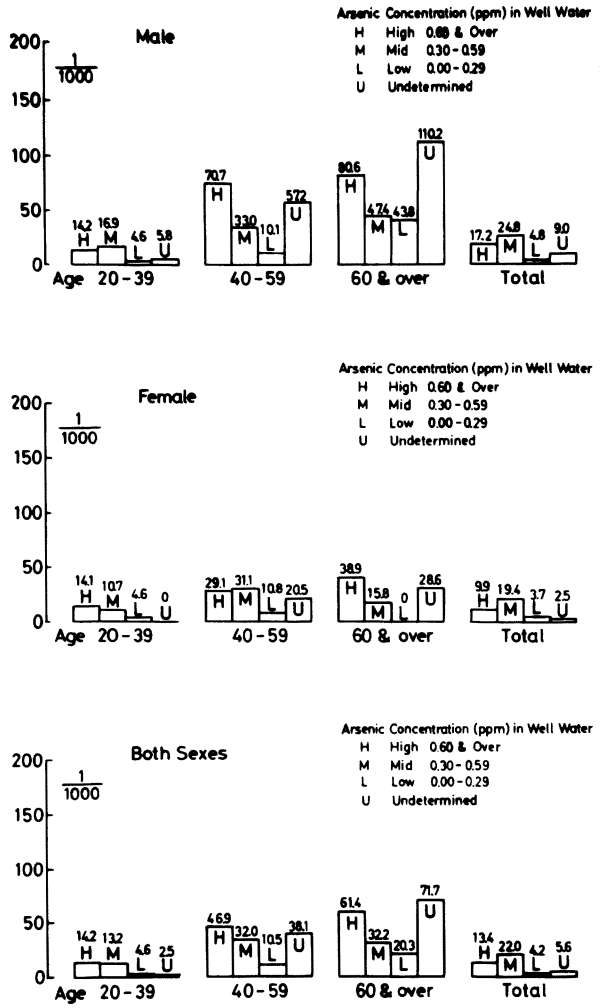

FIGURE 6. Age-specific and sex-specific prevalence rate per 1000 for blackfoot disease by arsenic concentration in well water.

Relation of Water Supply to Blackfoot Disease

It was determined that all of the patients with blackfoot disease had consumed artesian well water before the onset of the disease and none of the residents of the endemic area who had consumed only surface water or water from shallow wells developed blackfoot disease. This appears to be because the shallow well water is almost free from arsenic (0.001–0.017 ppm). In some parts of these areas, a tap water supply was provided in 1956. The change in the frequency of blackfoot disease since that time is strong evidence supporting the arsenic hypothesis. As shown in Table 3, in all periods studied—1955 and before, between 1956 and 1965, and between 1966 and 1975—there was no statistical difference in the age distribution between the districts with water supplied by artesian well and artesian well with a changeover to tap water in 1956. There were, however, more young patients in the A group than in the B group during the period 1956–75. It should be particularly noted that while there were no cases less than 20 yr old present in the B group, there were five cases in this age group in the A group during 1956–75. This fact is most important, since it shows that no cases were found among the inhabitants who were born after the tap water supply was established. These supplemental data support the conclusion that a close association exists between the consumption of arsenical water and the development of blackfoot disease.

Table 3. Incidence of blackfoot disease by age for areas served by different water sources for various onset periods.

	Incidence of blackfoot disease								
	1955 and before[a]			1956-1965[b]			1966-1975[c]		
water supply	<40 yr	≥40 yr	Total	<40 yr	≥40 yr	Total	<40 yr	≥40 yr	Total
Artesian well	75	75	150	117	292	409	38	203	241
Artesian well changed to tap water in 1956	41	25	66	39	113	152	8	82	90
Total	116	100	216	156	405	561	46	285	331

[a] $\chi^2 = 2.71$, $0.10 < p < 0.90$.
[b] $\chi^2 = 0.48$, $0.10 < p < 0.90$.
[c] $\chi^2 = 2.59$, $0.10 < p < 0.90$.

Hypothesis of the Cause of Blackfoot Disease

The hypothesis is: the occurrence of endemic blackfoot disease is directly related to the arsenic content of artesian well water.

The patients with blackfoot disease were classified into one of the three groups according to the arsenic concentration in the well water: high, mid, and low groups. A definite gradient was associated with the degree of exposure to arsenic (Table 4). Furthermore, with each cohort (duration of intake of arsenical water) a gradient in blackfoot patients was associated with degree of arsenic concentration. During of intake of arsenical water and degree of arsenic concentration were directly related and the difference was statistically significant ($\chi^2 = 11.53$, $n = 4$, $0.025 < p < 0.01$). Thus exposure to arsenic was found to be associated with an excess of frequency of blackfoot disease in the high exposure group of longer consumption of artesian well water. Thus, the hypothesis is sustained.

Degree of Severity in Relation to Duration of Intake of Arsenical Water at the Time of Onset

Table 5 shows that the group showing 0% impairment increased and the 1–4%, 5–24% and

Table 4. Incidence of blackfoot disease by duration of intake of arsenical water and degree of arsenic concentration.[a]

Duration of intake of arsenical water, yr.	Incidence of blackfoot disease			
	Low As (0–0.29 ppm)	Mid As (0.30–0.59 ppm)	High As (>0.60 ppm)	Total
<20	7	41	36	84
20–39	15	101	78	194
>40	77	284	164	525
Total	99	426	278	803

[a] $\chi^2 = 11.53$, $n = 4$, $0.025 < p < 0.01$.

Table 5. Degree of severity in relation to duration of intake of arsenical water at the time of onset.[a]

Duration of intake of arsenical water, yr	No. (%) showing various degrees of impairment						
	0%	1-4%	5-24%	25-49%	50-74%	75+ %	Total
0-19	30 (24.8)	20 (16.5)	30 (24.8)	32 (26.4)	8 (6.6)	1 (0.8)	121
20-39	118 (47.8)	36 (14.6)	50 (20.2)	28 (11.3)	11 (4.5)	4 (1.6)	247
40+	239 (32.2)	79 (10.7)	133 (17.9)	211 (28.5)	73 (9.9)	5 (0.7)	741
Total	387 (34.6)	135 (12.4)	213 (18.6)	271 (25.1)	92 (8.4)	10 (0.9)	1108

[a] $\chi^2 = 55.03$, $n = 10$, $p < 0.001$.

25–49% groups decreased in the 20–39 yr period of intake of arsenical water at the time of onset. From this, it can be supposed that this is a chronic type in which disease goes on gradually. Thereafter cases with both 25–49% and 50–74% impairment increased tremendously at ≥40 yr intake of arsenical water prior to time of onset. In general, the degree of permanent impairment of patient is significantly correlated with duration of intake of arsenical water at the time of onset ($\chi^2 = 55.03$, $n = 10$, $p < 0.001$).

As an aside, it may be noted that there is an acute type of reaction; the patient develops (severe impairment suddenly after a prolonged period of intake of arsenical water prior to the time of onset. Generally speaking, group in which the duration of intake of arsenical water at the time of onset was below 19 yr did not correlate with the permanent impairment in the 0%, 1–4%, 5–24%, and 25–49% impairment groups. Those account for 24.8%, 16.5%, 24.8%, and 26.4%, respectively. This fact indicates that there is an acute type which develops rather severe impairment in a shorter duration of intake of arsenical water at the time of onset.

Degree of Severity of Blackfoot Disease Related to Duration of Intake of Arsenical Water

As shown in Table 6, it is also true that the degree of permanent impairment is, in general, closely correlated with duration of intake of arsenical water, especially in severe cases. The percentage of impairment in 60 yr is much lower than that of the patients ingesting arsenical water for less than 40 yr. On the contrary, the percentage of moderate impairment increased with longer duration of intake of arsenical water. The differences of percentage of permanent impairment among different period of intake of arsenical water were statistically significant ($\chi^2=34.17$, $n=15$, $p<0.005$). Thus the degree of permanent impairment of patients with blackfoot disease was noted to be directly related to duration of intake of arsenical water.

Table 6. Degree of severity in relation to duration of intake of arsenical water.[a]

Duration of intake of arsenical water, yr	No. (%) showing various degrees of impairment						
	0%	1-4%	5-24%	25-49%	50-74%	75+ %	Total
0-19	30 (40.5)	13 (16.6)	14 (18.9)	13 (16.6)	3 (4.1)	1 (1.4)	74
20-39	104 (43.5)	31 (13.0)	48 (20.1)	43 (18.0)	10 (0.4)	3 (1.3)	239
40-59	186 (34.4)	55 (10.1)	98 (18.0)	145 (26.7)	54 (9.9)	5 (0.9)	543
60+	67 (26.6)	36 (14.3)	53 (21.0)	70 (27.8)	25 (9.9)	1 (0.4)	252
Total	387 (34.9)	135 (12.2)	213 (19.2)	271 (24.5)	92 (8.3)	10 (0.9)	1108

[a] $\chi^2 = 34.17$, $n = 15$, $p < 0.005$.

Mean Age at Death of Patients with Blackfoot Disease and Arsenic Level in the Well Water

Of the 528 deaths, for 379 patients with blackfoot disease, the mean age of death was found to be 58 ± 12.6 yr, 60.0 ± 12.7 yr, and 63.7 ± 12.2 yr, respectively, for high, mid, and low As levels (Table 7). The difference of mean age at death between high and low groups was statistically significant ($p<0.01$). The mean age of death for patients with blackfoot disease was significantly lower in areas of high arsenic content than in areas of low arsenic content of the well water.

Table 7. Age at death of patients with blackfoot disease by arsenic level in the well water.

As concn in well water[a]	Age at death, yr								
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+	Total
High (1)	1	0	3	5	23	31	42	22	127
Mid (2)	1	0	4	8	23	59	64	44	203
Low (3)	0	0	2	1	2	7	21	16	49
Total	2	0	9	14	48	97	127	82	379

[a] t_{1-2}: $p = 0.147$, NS, t_{1-3}: $p = 0.006$, $p < 0.01$; t_{2-3}: $p = 0.062$, NS.

Case Fatality of Patients with Blackfoot Disease

The relationship between age at onset and subsequent fatality is shown in Table 8. The greatest concentration of age at onset was in the 50–59 age group. The case-fatality rate increased linearly with age at the time of onset, with greater risk for older patients, reaching 66.3% by 70 yr or over, in general, the older the age group the higher the rate.

Table 8. Case-fatality according to age at onset.

Age, yr	No. of patients	No. dying	Case-fatality rate, %
1–9	26	7	26.9
10–19	85	20	23.5
20–29	89	20	22.5
30–39	150	50	33.3
40–49	216	111	51.4
50–59	258	139	53.9
60–69	195	122	62.6
70+	89	59	66.3
Total	1108	528	47.7

Causes of Death in Patients with Skin Cancer and Patients with Blackfoot Disease

During the follow-up period of 18 yr for blackfoot disease, 528 of 1108 patients died. This is an overall fatality rate of 47.7%. Another 10-yr follow-up period for skin cancer showed 244 of 428 patients died, giving a 57.0% fatality rate.

An analysis was made of the causes of death up to 1975 in patients with these two diseases as compared with that in the general population of the endemic area((Table 9). The most common cause of death in patients with skin cancer or blackfoot disease was carcinoma of various sites, 27.9% in skin cancer and 18.8% in blackfoot disease. Cardiovascular disease was also responsible for 15.7% of death in patients with blackfoot disease. In general, in the population of the endemic area in 1966, cancer accounted for 13.1% of the deaths and cardiovascular disease 9.1%, whereas for the whole population of Taiwan in 1966 cancer and cardiovascular disease accounted for 7.9 and 8.1% of cases, respectively.

Death Rate of Patients with Blackfoot Disease

Table 10 shows the death rate among the patients with blackfoot disease. An annual death rate per 1000, as might be expected, increased somewhat with age, 528 deaths in 12,461 patient-years in this series give an annual death rate of 42.4 per 1000.

Table 9. Causes of death in patients with skin cancer and patients with blackfoot disease.

	Skin cancer patients		Blackfoot disease patients		General population in endemic area	
Cause of death	No.	%	No.	%	No.	%
Cancer	68	27.9	99	18.8	125	13.1
Lung	15	6.1	21	4.0	21	2.2
Skin	15	6.1	12	2.3	3	0.3
Bladder	10	4.1	17	3.2	16	1.7
Liver	6	2.5	21	4.0	17	1.8
Colon	5	2.0	3	0.6	12	1.3
Kidney	5	2.0	—	0	—	0
Stomach	3	1.2	4	0.8	13	1.4
Nasal cavity	2	0.8	5	0.9	16	1.7
Bone	2	0.8	4	0.8	2	0.2
Uterus	1	0.4	2	0.4	6	0.6
Esophagus	—	0	4	0.8	2	0.2
Miscellaneous	4	1.6	6	1.1	17	1.8
Cardiovascular disease	30	12.3	83	15.7	87	9.1
Gangrene	7	2.9	70	13.3	—	0
Cerebrovascular disease	32	13.1	63	12.0	91	9.6
Respiratory disease	46	18.9	100	18.9	231	25.1
Pulmonary tuberculosis	10	4.1	41	7.8	55	5.8
Pneumonia	17	7.0	28	5.3	117	12.3
Others	19	7.8	31	5.9	67	7.0
Disease of the alimentary tract	13	5.3	34	6.4	118	12.4
Senility	12	4.9	22	4.2	50	5.3
Renal disease	7	2.9	21	4.0	34	3.6
Miscellaneous	13	5.3	30	5.7	207	21.8
Unknown	16	6.6	6	1.1	—	0
Total	244		528		951	

Table 10. Calculation of death rates specific for age for blackfoot disease (based on patient-years).

Age at onset, yr	No. of patients	Patient-years at risk	No. of deaths	Annual death rate per 1000
1-9	26	545	7	12.8
10-19	85	1869	20	10.7
20-29	89	1572	20	12.7
30-39	150	2279	50	21.9
40-49	216	2588	111	42.9
50-59	258	2207	139	45.2
60-69	195	1108	122	110.1
70+	89	293	59	201.4
Total	1,108	12,461	528	42.4

Survival Rate of Patients with Blackfoot Disease

Survival rate represents the period of time between the onset of disease and the end of the study. Figure 7 shows the survival rate each year after the onset of disease for amputated, nonamputated, and total patients. The 5-yr survival rates after onset of blackfoot disease for total, amputated, and nonamputated patients were 76.3%, 73.5%, and 80.9%, respectively. The 10-yr survival rates were 63.3%, 60.0%, and 68.8%, respectively; 15-yr survival rate,

52.2%, 48.2%, and 60.0%, respectively. The 50% survival point for total, amputated, and nonamputated patients were 16, 14, and 21 yr, respectively. The annual death rate per 1000 by the end of 15 yr was 51.6 per 1000 in amputated patients, 38.1 per 1000 in nonamputated patients, and 46.0 per 1000 in total blackfoot patients. It must be pointed out that many factors, such as duration of intake of arsenical water, may influence the results.

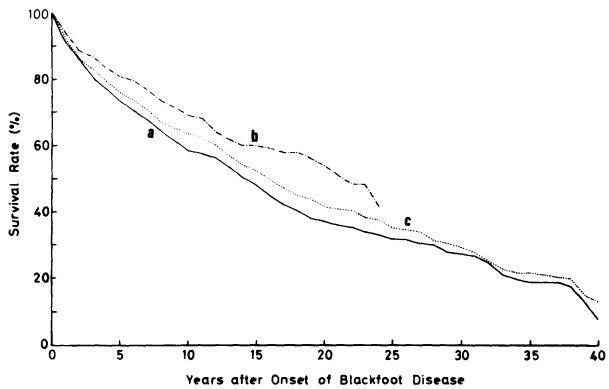

FIGURE 7. Survival rate of patients with blackfoot disease: (*A*) amputated patients; (*B*) nonamputated patients; (*C*) total patients.

Survival Rate of Patients with Blackfoot Disease Related to Duration of Intake of Arsenical Water

It is also worthwhile to give special consideration to the relationship between the survival rate and the duration of intake of arsenical water. The duration of intake of arsenical water was divided into four groups; 1–19 yr, 20–39 yr, 40–59 yr, and >60 yr. As shown in Figure 8, there was a clear-cut descending gradient of survival rate from the >60 yr group to 40–59 yr group to the 1–19 yr group. The 50% survival points for patients with 1–19, 20–39, 40–59, and >60 yr intake of arsenical water were 25, 31, 14, and 5 yr, respectively. Annual death rates per 1000 by the end of 15 yr were 5.9 per 1000 in the 1-19 yr intake group 14.7% per 1000 in the 20–39 yr group, 50.8 per 1000 in the 40–59 yr group and 112.2 per 1000 in the >60 yr group.

Discussion

Although arsenic is notorious primarily for its acute toxicity, chronic toxicity is also a problem. Despite the many papers dealing with the medical, dietary, and occupational etiology of arsenical cancer, no reliable data on the frequency of arsenical cancer in a total population at risk are available in the literature. Arsenic is a common mineral, and

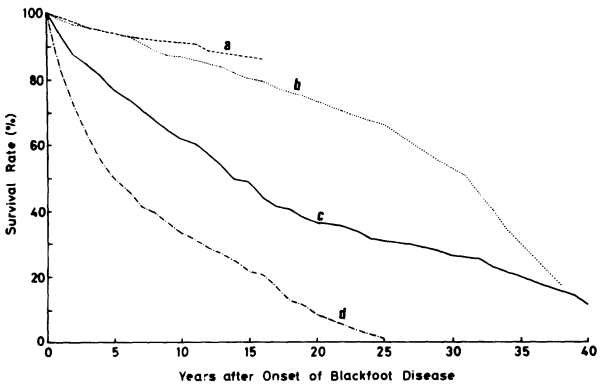

FIGURE 8. Survival rate of patients with blackfoot disease in relation to duration of intake of arsenical water: (*A*) 0-19 yr; (*B*) 20-39 yr; (*C*) 40-59 yr; (*D*) >60 yr.

in many parts of the world it appears in drinking water obtained from wells drilled into arsenic-rich ground strata. The classical examples of toxicity from consumption of arsenic-polluted public drinking water are presented by the occurrence of skin cancer in members of some population groups, residing in the district of Reichenstein, Silesia, Poland (*7*), in Cordoba Province, Argentina (*10*) and recently in Antofagasta, Chile (*11*). Although a positive association between the arsenic level of drinking water and the prevalence of skin cancer in endemic areas of chronic arsenicism has been reported from the above-mentioned area, a negative finding was also noted in Lane County, Oregon, U. S. (*24*). The Lane County water arsenic levels averaged much lower than those reported from Taiwan and Antofagasta (*11*), so that they suggested that their increasing incidence of basal cell carcinoma might be potentiated by urban air pollutants.

Skin cancer, which is very common in Caucasians, has a relatively low incidence among Chinese in Taiwan—only 2.9% (*25*). Skin cancers usually occur on exposed surfaces, i.e., on the head, face, and extremities, and often are epidermoid or basal cell carcinomas. These features are also present in patients with ordinary skin cancers in Taiwan, but do not appear in the present series of arsenical cancer cases. The most common type of lesion (*26*) was intraepidermal carcinoma (51.7%), and the body areas most frequently involved were unexposed surfaces (74.5%). In addition, the extremely high percentage of cases with multiple skin cancer (99.5%) was characteristic of our series.

In general, the prevalence of skin cancer, hyperpigmentation, and keratosis increased steadily with age. As the inhabitants of the endemic area started using artesian wells for drinking water more than 55 yr ago, the period of exposure to arsenic-polluted

water was very long in those who were over age 50 at the time of examination. It was difficult to elicit from patients the age at onset of arsenical cancer, because most of the patients were unable to name a date. We know from this study that the youngest cancer patient was 25, the youngest with hyperpigmentation was 5, and the youngest with keratosis was 15. This means that hyperpigmentation can occur in patients who have been exposed for at least 5 years, keratosis for 14 yr, and cancer for 24.

There was a similar finding for blackfoot disease, which occurred in 8.9 per 1000 population. Histologically, blackfoot disease can be divided into two reaction groups, arteriosclerosis obliterans and thromboangiitis obliterans. The fundamental vascular change in both groups is severe arteriosclerosis leading to arteriosclerotic gangrene in 69.2% (*3*). Peripheral circulatory disorders occasionally occur in chronic arsenicism (*5–9*). At least 15 cases of chronic arsenicism have been reported with gangrene of the extremities (*5, 7, 8, 13–19*). Only two of them were females. The age ranged from 33 to 54. Although detailed pathological observations on autopsy specimens or amputated limbs are lacking in the cases reported, the gangrene appears to result from arteriosclerosis and thromboangiitis obliterans (*5*). Is arsenic an agent capable of eliciting arteriosclerosis? Hueper (*27*), in a comprehensive review of the subject of arteriosclerosis, has outlined arsenic as one of the vasodilating depressors. Chronic exposure to arsenical compounds may result in gangrene of extremities which he thought of as the equivalent of focal anoxemic myocardial and cerebral necrosis caused by those agents which exert their main vasodilating effects on the cerebral and coronary arteries.

A dose-response relationship between blackfoot disease and the arsenic level of drinking water was similar to that observed for skin cancer. One final source of evidence to support this positive association is obtained when one examines the frequency of blackfoot disease among young children who were born after the tap water supply was established in 1956. No new cases have been found among those children less than 20 yr old in the area supplied with tap water. However people who changed to tap water could still be affected with blackfoot disease if they had a previous history of drinking artesian well water.

The duration of intake of arsenical water also much influences the severity of permanent impairment of the extremities, mean age at death, and survival rate of patients with blackfoot disease. We found that the association of blackfoot disease with hyperpigmentation, keratosis, or skin cancer was not a coincidental or chance occurrence, which strengthened the likelihood of a causal relationship between blackfoot disease and chronic arsenicism. This leads to the conclusion that skin cancer and blackfoot disease are both part of the entity of chronic arsenicism.

REFERENCES

1. Yeh, S. Relative incidence of skin cancer in Chinese in Taiwan—with special reference to arsenical cancer. In: National Cancer Institute, Monograph 10, U. S. Government Printing Office, Washington, D. C. 1963, pp. 81–107.
2. Tseng, W. P., et al. A clinical study of blackfoot disease in Taiwan, an endemic peripheral vascular disease. Mem. College Med. Nat. Taiwan Univ. 7: 1 (1961).
3. Yeh, S., and How, S. W. A pathological study on the blackfoot disease in Taiwan. Repts. Inst. Pathol. Nat. Taiwan Univ. No. 14: 25 (1963).
4. Neubauer, O. Arsenical cancer—a review. Brit. J. Cancer, 1: 192 (1947).
5. Butzengeiger, K. H. Über periphere Zirkulationsstörungen bei chronischer Arsenvergiftung, Klin. Wochenschr, 19: 523 (1940).
6. Butzengeiger, K. H. Die chronische Arsenvergiftung der Winzer, Ärzt. Wochenschr, 4: 365 (1949).
7. Geyer, L. Über die chronischen Hautveränderungen beim Arsenicismus and Betrachtungen über die Massennerkrankungen in Reichenstein in Schlesien. Arch. Dermat. Syph., 43: 221 (1898).
8. Roth, F. Über die chronische Arsenvergiftung der Moselwinzer unter besonderer Berücksichtigung des Arsenkrebses. Z. Krebsforsch., 61: 287 (1956).
9. Zinny, M., and Vivaldo, J. C. El arsenicisno cronico evidemic por las aguas de consumo. Rev. Med. Rosario, 16: 187 (1926).
10. Arguello, R. A., Cenget, D. D., and Tello, E. E. Cancer and regional endemic chronic arsenicism. Brit. J. Derm. 51: 548 (1939).
11. Zaldívar, R. Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. Beitr. Pathol., 151: 384 (1974).
12. Hueper, W. C. Environmental factors in the production of human cancer. In: Cancer. R. W. Raven, Ed., Butterworths, London, 1957, Vol. 1, p. 438.
13. Cannon, A. B. Chronic arsenical poisoning; symptoms and sources. N. Y. J. Med., 36: 219 (1936).
14. Dürck, Y. Die pathologische Anatomie im Dienste der Unfallbegutachtung. München Med. Wochenschr. 84: 81 (1937).
15. Kotzing. Sammlung von Vergiftungsfällen Vol. 6, 1935.
16. Kraetzer, A. F. Raynaud's disease associated with chronic arsenical retention; report of case cured by sodium thiosulphate, J.A.M.A. 94: 1035 (1930).
17. Kren, O. Aussprache. Wien. Klin. Wochenschr, 1: 476 (1930).
18. Oppenheim, M. Hauterkrankung durch arsenhaltigen Mauerabstrich. Wien. Klin. Wochenschr, 1: 475 (1930).
19. Strauss, F. Extremitätengangrän. Arch. Klin. Chir., 173: 92 (1932).
20. Kuo, T. Arsenic content of artesian well water in endemic area of chronic arsenic poisoning. Repts. Inst. Pathol. Nat. Taiwan Univ. No. 20: 7 (1968).
21. Yeh, S. Skin cancer in chronic arsenicism, Human Pathol. 4: 469 (1973).
22. Natelson, S. Microtechniques of clinical chemistry, 2nd ed., Charles C Thomas, Springfield, Ill., 1961, pp. 113–119.

23. Committee on Rating of Mental and Physical Impairment. Guides to the evaluation of permanent impairment of the extremities and back. J.A.M.A., Spec. Ed., February 15, 1958.
24. Morton, W., et al. Skin cancer and water arsenic in Lane County, Oregon. Cancer 37: 2523 (1976).
25. Yeh, S. Some geographic pathology aspects of common diseases in Taiwan. Part Two. Infection and cancer. Internat. Path., 7: 24 (1966).
26. Yeh, S., How, S. W., and Lin, C. S. Arsenical cancer of skin: histological study, with special reference to Bowen's disease. Cancer 21: 312 (1968).
27. Hueper, W. C. Arteriosclerosis. a general review. Arch. Pathol. 38: 162, 245, 350 (1944); ibid. 39: 51, 117, 187 (1945).