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JOURNAL TITLE: American Med. Ass. ARCH IND HYG OCCUP MED

VOLUME, NUMBER, PAGES, YEAR: 4:199-205, 1951.

AUTHOR: SNEGIREFF LS AND LOMBARD OS

TITLE: ARSENIC AND CANCER OBSERVATIONS IN THE MET ALLURGIC INDUSTRY

INTERLIBRARY LOAN? YES
SOURCE: JJNCI 42:1045-1052, 1969.

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ARSENIC AND CANCER

Observations in the Metallurgical Industry

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THE THEORY that arsenic may cause cancer dates back 130 years to the writings of Paris.[1] These have been quoted many times over by medical writers, who at times have credited Paris with unfounded additions, as ably pointed out by Kennaway.[2] The suspicion still appears to exist that arsenic may cause cancer in healthy humans. The whole subject was recently reviewed in behalf of the Arsenic Committee of the Medical Research Council in Great Britain by Neubauer.[3]

In the light of recent experience with multiple factors in carcinogenesis [4] it is well to reconsider this subject.

Arsenic compounds are among the oldest known to medicine for their treatment properties. Arsenic is a component of the earth's crust, and a certain amount of it is constantly released in dust form. As rocks, containing varying amounts of arsenic, break down and disintegrate to form soils, a like percentage of arsenic contained in the rock is inherited by the soil. In a study of soil distribution of arsenic, Williams and Whetstone [5] made determinations on samples which were widely distributed geographically and were chosen to represent the great soil groups. Arsenic was found in all samples of normal soil examined and ranged in quantity from a fraction of a part per million (ppm) to about 40 ppm. The plants examined likewise contained variable amounts of arsenic. Coulson, Remington, and Lynch [6] found as high as 130 ppm of arsenic in the edible portion of a shrimp.

Presented at the Annual Meeting of the Industrial Hygiene Foundation, Pittsburgh, Nov. 15, 1950.

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1. Paris, J. A.: Pharmacologia, ed. 3, London, W. Phillips, 1820.

2. Kennaway, E. L.: Contribution to Mythology of Cancer Research, Lancet 2:769-722 (Dec. 26) 1942.

3. Neubauer, O.: Arsenical Cancer: A Review, Brit. J. Cancer 1:192-251, 1947.

4. Berenblum, I.: Cocarcinogenesis, Brit. M. Bull. 4:343-345, 1947. Crabtree, H. G.: Anti-Carcinogenesis, ibid. 4:345-348, 1947.

5. Williams, K. T., and Whetstone, R. R.: Arsenic Distribution in Soils and Its Presence in Certain Plants, Technical Bulletin 732, United States Department of Agriculture, 1940.

6. Coulson, E. J.; Remington, R. E., and Lynch, K. M.: Metabolism in the Rate of Naturally Occurring Arsenic in Shrimp as Compared with Arsenic Trioxide, J. Nutrition 10:225-270, 1935.

Chapman [7] found that shellfish and crustaceans from the coastal waters of the British Isles showed an arsenic content range from 2.3 ppm in oysters to 132 ppm in prawns.

Thomas and Collier [8] have shown that the smoke of cigarets, as well as that of cigars and pipe tobacco, contains approximately 30 to 100 ppm as originally present in the tobacco products. The concentration of arsenious oxide in puffed smoke ranges from 0.2 to 3.0 mg. per cubic meter with cigars, 1.7 to 5.7 mg. per cubic meter with pipe tobacco and 3.3 to 10.5 mg. per cubic meter with cigarets. This would indicate that humans cannot escape contact with arsenic, which has always existed in nature and was ingested by our ancestors for generations past even as it is in our civilized society today.

It is not within the scope of this paper to discuss the relative ranges of absorption of water-soluble arsenicals or the rates at which they are stored or eliminated by the human body in health and in disease; suffice it to say that much of the apparent confusion which surrounds this subject may be attributed to the lack of refined laboratory methods which could help in the interpretation of clinical reports citing instances of observed association of keratoses or carcinomas and prolonged arsenical therapy.

Franseen and Taylor [9] and others have stated that in psoriasis as in other systemic diseases with or without prior skin manifestations, after a number of years of treatment with potassium arsenite solution (Fowler's solution), keratoses and carcinomas were observed. However, Mattice and Weisman [10] pointed out that frequently ascribing of pathological states to chronic arsenic intoxication is based on assumption rather than on arsenic determinations made under controlled conditions. This raises the point of the other multiple factors concerned with carcinogenesis in persons who have upset cellular metabolism, as manifested by signs of systemic disease for which arsenicals were prescribed in the first place. In another group of patients reported in medical literature skin changes have developed, ranging from pigmentation and warty growth to keratosis and epithelioma. There is a numerical paucity of reports of such cases in modern medical literature, where arsenic effect is suspected on the basis of anatomical distribution of lesions on fingers and toes. For as Kennaway [11] pointed out 25 years ago, there has been much confusion between epitheliomas attributable to pitch and to arsenic. The paucity of reports is even more evident when compared with the magnitude of arsenic distribution in nature, and the everyday exposure of humans to it in the course of the day's activities, as well as in the production and mass utilization of purified arsenic in industry. There are indications that biologically the human race made the adjustment to arsenic in the environment and that only rarely, when associated with

7. Chapman, A. C.: On the Presence of Compounds of Arsenic in Marine Crustaceans and Shell Fish, Analyst 51:548-563, 1926.

8. Thomas, M. D., and Collier, T. R.: Concentration of Arsenic in Tobacco Smoke Determined by Rapid Titrimetric Method, J. Indust. Hyg. & Toxicol. 27:201-206, 1945.

9. Franseen, C. C., and Taylor, G. W.: Arsenical Keratoses and Carcinomas, Am. J. Cancer 22:287-307, 1934.

10. Mattice, M. R., and Weisman, D.: Urinary Excretion of Arsenic in Normal Subjects, Am. J. M. Sc. 193:418-419, 1937.

11. Kennaway, E. L.: The Anatomical Distribution of the Occupational Cancers, J. Indust. Hyg. 7:69-93, 1925.

other contributing endogenous factors such as systemic disease, or possibly exogenous factors, such as radiation, it may be capable of upsetting the biological equilibrium.

Stern and Willheim [12] suggested the apparent ambivalence of arsenic as a treatment agent and as a factor contributing to the development of cancer in susceptible persons, which may be likened to the effects of x-rays. This statement should be considered in the light of clinical experience with skin cancers following use of potassium arsenite solution and later treatment with x-ray which eventually break down and require surgical amputation. There is a parallel experience with overexposures to x-ray and radium in early workers. It is because of the above circumstances that we became interested in this subject.

METHODS AND PLANS OF INVESTIGATION

In spite of great interest in the industrial carcinogens there are no satisfactory biological or chemical tests of cancer susceptibility that may be applied to humans. For that reason, our approach to the problem was considered from the biostatistical standpoint.

Since arsenic is widely distributed in nature, we felt that the best place to study the untoward effects would be in the metallurgical industries where quantitative exposures over many years can be observed in those who handle arsenical compounds, such as arsenic trioxide.

Through the good offices of our colleague, Prof. Philip Drinker, one of us (L. S. S.) obtained permission to visit a number of plants in the United States and outside its borders and to have access to records of the medical departments, the personnel files, employment information, death records, and other data pertinent to this study. During the field visits the personnel of the medical and safety departments of the several plants visited assisted in checking the clinical and death records of employees, in obtaining medical histories, and conducting clinical examinations on workmen selected particularly for their long-term employment in the arsenic production, including the controls. The principal objective of the survey reported here was to ascertain whether arsenic played a significant role reflected in the cancer mortality among the employees of the plants.

The data from the arsenic and control plants located in the continental United States were regrouped for comparison with the corresponding population and mortality data available through published official reports of the United States Bureau of Census and the United States Public Health Service. The data were subjected to statistical tests for the determination of their significance.

Field observations were made and recorded at the time of the visits of one of us (L. S. S.) to plants in June through September, 1949. These observations formed the basis for the evaluation of statistical data in the light of "on the spot" working conditions and environmental influences in the plants surveyed. In each place volunteers who had worked in arsenic for many years were physically examined and interviewed in the presence of the plant physician or of a responsible member of the administrative staff. Thus we were able to see the persons who should have shown the most profound effects of exposure to arsenic.

12. Stern, K., and Willheim, R.: The Biochemistry of Malignant Tumors. Brooklyn, N. Y., The Chemical Publishing Company, Inc., 1943.

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Our principal difficulty was encountered in the plants abroad, where there is no dearth of excellent statistical information in the company records pertaining to plant population by categories, length of service, morbidity due to arsenicalism, and the general state of health of the employees, but where one can place little credence in the reported causes of death and where the general population statistics are unreliable. Hence, after sorting the data, we discarded all that we collected in the plants outside the continental United States. This is no reflection on record-keeping methods in the plants we visited. It is, simply, our desire to use conservative valid data that we can compare geographically by units.

From what has been said it is possible to appreciate the difficulty of an exact interpretation of statistical observations. Among the obstacles are the so-called multiple factors. These may be visualized as several specific forces exerting a biological impact on man. Very often such forces act together, simultaneously, and their individual quantitative effects are hard to separate. The biologist is therefore forced to make certain assumptions which he believes to be true and which are based on accepted biological principles or laws.

In inductive statistics an attempt is made to apply to the universe the findings of a sample. It is important to separate differences or relationships due to chance from the real differences and relationships. The majority of applicable statistical procedures were tried in this attempt, as exemplified by chi-square tests.

The result of a test of significance of two probabilities is important or borderline according to the yardstick used by the observer. For example, by chance alone a phenomenon could occur once in 20 times. The probability of 0.05 in a chi-square table is significant statistically if 0.05 is considered the criterion of significance. Statisticians using the one-in-20 chance as a criterion of significance would say that something besides chance is entering into the picture.

In order to understand the biological impact exerted by arsenic on humans it is well to remember what we have said earlier about cancer.

FINDINGS

During the previous 25 years 18 deaths were recorded from cancer among employees at Plant A (Table 1). It was noted that seven of these were ascribed to cancer of the respiratory system, which appeared sporadically throughout the plant without any apparent pattern of distribution, nor were these deaths limited to any specific occupational group within the plant. It appears that it is this sporadic occurrence of cases that has led some physicians to attribute a causal relationship of cancer to arsenic exposure. As Macklin[13] pointed out, if we are looking for causal proof we can certainly find it if we look long enough. However, the real problem is to ascertain whether this is statistically significant or whether it is an invitation to draw a false conclusion.

Let us examine the facts summarized in the table. The ratio between the cancer deaths and the total deaths in an area represents the relative importance of the cancer problem in the area. Thus it can be seen that Plant A appears to have a

13. Macklin, M. T.: Pitfalls in Dealing with Cancer Statistics, Especially as Related to Cancer of the Lung, Dis. Chest 14:525-528, 1948.

slightly higher proportionate mortality than the state. Whether the difference is real or only chance fluctuation, which might be reversed in another sample, must be determined.

The method employed to establish whether a difference is real or merely a chance fluctuation is determined by the type and the quantity of the data. In Plant A the proportionate mortality for the age group "under 55" is 12.5%, over twice the corresponding value for the state as a whole. Thus, on inspection alone, Plant A appears to have proportionally many more cancer deaths than the state, but this proportion is based on only nine cancer deaths among 72 deaths from all causes, while the state figure is based on 1,656 deaths from cancer among 27,164 deaths

TABLE 1.—*Cancer Deaths, Total Deaths, and Cancer Deaths per Hundred Total Deaths for Males by Age and Locality (Various Years)*
(Large quantities of arsenic trioxide are handled at Plant A)

	Plant A*			State†		
Age	Cancer Deaths	Total Deaths	Cancer Deaths per 100 Total Deaths	Cancer Deaths	Total Deaths	Cancer Deaths per 100 Total Deaths
Under 55	9	72	12.5	1,656	27,164	6.1
55-64	8	48	16.7	1,821	12,368	14.7
65-74	1	20	5.0	2,025	13,100	13.4
75-..	0	6	0.0	1,536	15,949	9.6
Unknown	..	..	....	10	142	....
Total	18	146	12.3	7,048	70,732	10.0

Age	Cancer Deaths Observed	Cancer Deaths Expected (E)‡	O-E	(O-E)²	$\frac{(O-E)^2}{E}$
Under 55	9	4.4	4.6	21.16	4.8
55-64	8	7.1	0.9	0.81	0.1
65-..	1	3.0	−2.0	4.00	1.3
Total	18	14.5	3.5	.....	6.2 = X²

* The years covered in Plant A were those from 1922 to 1949.
† The figures for the state are weighted for the years when the cancer deaths occurred at Plant A.
‡ $E = Pr_i \times D_i$

Where Pr_i = proportionate mortality for the state by age.
D_i = total deaths for the plant by age.
n = 3 O = Observed, E = Expected.
P = approximately 0.10, which is not significant.

from all causes. It is immediately evident that the figure for the state is much more stable than that for the plant.

By chance alone the nine cancer deaths might be expected to range between three deaths and 15 deaths in 19 of 20 samples, such as were observed in Plant A; and once out of the 20 samples the number of deaths could by chance be greater than 15 or less than 3. Thus the proportionate mortality of 12.5% evidenced in Plant A might have been actually less than the 6.1% observed for the state.

This technique lends itself to the testing of the differences in different age groups as well as the differences in plants. We compared the plant as a whole with a hypothetical distribution of deaths. This was done by assuming that the plant should evidence the proportionate mortality in the given age groups which was observed

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in the state. On this assumption an expected number of cancer deaths was obtained for the plant by multiplying the state proportionate mortality for cancer in each age group by the corresponding number of total deaths which occurred in the plant. The observed distribution of cancer deaths was compared with the expected distribution of cancer deaths by means of the chi-square test. On the basis of this test the numbers of cancer deaths in Plant A showed no evidence of significant difference from the state values.

For contrast with plants handling arsenic, we have chosen Plant Z, where working conditions approximate those of Plant A except that no arsenic is handled. During the last 10 years there were observed among the employees at Plant Z 12

TABLE 2.—*Cancer Deaths, Total Deaths, and Cancer Deaths per Hundred Total Deaths for Males by Age and Locality (Various Years)*
(Plant Z does not handle arsenic)

Age	Plant Z * Cancer Deaths	Plant Z * Total Deaths	Cancer Deaths per 100 Total Deaths	State † Cancer Deaths	State † Total Deaths	Cancer Deaths per 100 Total Deaths
Under 55	3	36	8.3	916	16,136	5.7
55-64	3	24	12.5	984	7,112	13.1
65-74	3	25	12.0	1,108	7,334	12.9
75-	3	24	12.5	700	6,804	10.3
Unknown	..	..	....	1	22	....
Total	12	109	11.0	3,654	38,018	9.6

Age	Cancer Deaths Observed	Cancer Deaths Expected (E)‡	O-E	$(O-E)^2$	$\frac{(O-E)^2}{E}$
55	3	2.0	1.0	1.00	0.5
55-64	3	3.2	−0.2	0.04	0.0
65-	6	6.0	0.0	....	0.0
Total	12	11.2	0.8	....	$0.5 = \chi^2$

* The years covered in Plant Z were those from 1941 to 1949.
† State figures are allocated to place of residence.
‡ $E = P_{Ti} X D_i$

Where P_{Ti} = proportionate mortality for the state by age.
D_i = total deaths for the plant by age.
n = 3 O = Observed, E = Expected.
P = approximately 0.90, which is not significant.

deaths due to cancer. Of these, 6 were attributed to cancer of the lung. The same technique was applied to the cancer problem in Plant Z (Table 2) as in Plant A (Table 1). The proportionate mortalities for the age groups under 55 showed a similar tendency to be higher in the plant than in the state.

SUMMARY AND CONCLUSIONS

For 130 years men have looked at arsenic as a possible cause of cancer. Today, in the light of our growing appreciation of the importance of chemical compounds as specific agents, each endowed with its characteristic biological properties, which are not to be taken for granted as being limited by group characteristics, and with a growing insight into the complex relationships of the multiple factors required to "spell" cancer, we are impressed by the unavoidable—that in some men who

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work in arsenical industries cancer will develop. There is, however, reasonable doubt that some arsenical compounds will cause cancer. In our study of Plant A, where large amounts of arsenic trioxide are handled, we found a slightly higher proportionate mortality from cancer among the employees than in the state-adjusted figures. But the same was found true of Plant Z, where arsenic is not handled but where the other factors are comparable. Statistical tests showed that these differences are chance fluctuations and are not significant.

On the basis of evidence examined in this preliminary survey we conclude that the handling of arsenic trioxide in the industry studied does not produce a significant change in the cancer mortality of the plant employees; hence other factors in addition to arsenic must be considered significant in the causal relationship to cancer.

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