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Carcinogenic, Teratogenic, and Mutagenic Effects of Arsenic

by Vladimír Bencko*

This review outlines briefly the history and present status of the problem of carcinogenic, teratogenic and mutagenic effects of arsenic. Discrepancies between clinical observations and positive results of epidemiological studies and the experimental induction of cancer by arsenic are discussed. The present knowledge of the mechanism of teratogenic and mutagenic effects of arsenic is analyzed.

The growing importance of arsenic as an environmental pollutant is demonstrated. Continuation of throughly organized epidemiological studies in regions with excessive arsenic exposure of the population and standardization of an epidemiological approach to this problem on an international basis are recommended. New approaches in experimental studies of the carcinogenicity of arsenic in combination with other known or suspected carcinogens are recommended as well.

Arsenic has long been thought to contribute to the incidence of cancer. In connection with the growing number of people exposed to this substance, occupationally as well as nonoccupationally in some areas, this becomes an important problem. The aim of this paper is to outline the history and present state of this problem and its possible solution. Some remarks concerning the mutagenic and teratogenic effects of arsenic are offered as well.

The occurrence of scrotal carcinoma among copper smelter workers in Cornwall (Wales) was described as early as 1820 by Paris (*1*), who regarded it as a consequence of exposure to arsenic fumes. Wilson (1896) noticed a relationship between multiple hyperkeratoses and arsenic exposure. Skin carcinomas occurring after long-term treatment with arsenic preparations were described by Hutchinson (*2*). A common feature of these carcinomas was the previous occurrence of multiple keratoses. Geyer (1898) described 65 skin carcinomas in Cordoba, where the contamination of drinking water by arsenic reached 0.45 mg As/l. (*3*). Lung carcinomas among miners at the Schneeberg mine were attributed to the arsenic in mine dust, its concentrations being about 1% (*4*), until 1932, when Pirchan and Sikl considered that this carcinoma might result from the radioactivity of the mind ores (*5*). It is possible that both agents contribute. The tendency of arsenical hyperkeratoses toward malignant degeneration was analyzed in a group of several hundred patients, with the resulting conclusion that at least 20% suffered from malignant disease (*6*). Neubauer (*7*) reviewed 143 published cases, of which 71% presented multiple carcinomas combined with a history of arsenic exposure; he remarked, however that in many cases other possible contributory factors were present. Černý and Neuman (*8*) demonstrated a highly suspicious relationship between arsenic and skin carcinoma. Neuman and Schwank (*9*) published considerable material which points irrefutably to arsenic as a causative factor in multiple keratoses and skin carcinomas. These authors stressed the needless risk of prescribing frequently useless arsenical drugs. In their collection of patients, the latency from initiation of treatment with arsenicals to the occurrence of carcinoma was in most cases more than 20 yr and, in one third of examined cases, more than 30 yr. These values correspond to those found in most of the literature. Chronic arsenic exposure has been implicated in the pathogenesis of angiosarcoma in German vineyard workers (*10*). Long-term medical administration of arsenic in the form of Fowler's solution has been implicated in two cases of angiosarcoma to date (*11*, *12*). The suspicion that arsenic can cause malignant degeneration of cells is the reason for which several authors stress the

*Department of General and Environmental Hygiene, Medical Faculty of Hygiene, Charles University, 10042 Prague, Czechoslovakia.

necessity to exclude arsenic from drugs used in human therapy. Such a prohibition is now in effect, e.g., in Czechoslovakia, where the use of arsenic preparations in human therapy is forbidden, with the exception of those applied in the treatment of protozoal infections.

Cancers of probable occupational origin have been reported in gardeners (*13*) and in vineyard workers (*14, 15*); in both cases, arsenic exposure was through the use of arsenical pesticides. The long-term mortality analysis in workers handling organic compounds of arsenic showed a higher incidence of carcinomas compared to the local population (*16, 17*). Workers who handled arsenicals exhibited marked pigmentations and hyperkeratoses with wartlike growths on exposed areas, and elevated arsenic levels in urine and hair. At the time of examination no arsenic-related cancer was found. Snegireff and Lombard (*18*) compared cancer incidence rates between factory workers with and without arsenic exposure. In spite of the evidence for the carcinogenicity of arsenic, there were no statistically significant conclusions, possibly because the examined groups were relatively small. Papers were published which demonstrated cases of carcinomas of internal organs after arsenic exposure (*19–28*). Recently (*29*) carefully performed epidemiological studies clearly demonstrate the likelihood of arsenic being carcinogenic.

Until recently, experimental attempts to induce "arsenical" carcinomas in animals either failed or were of very limited significance (*30–32*). Askanazi (*33*) noticed benign and malignant teratomas in rat embryos transplanted into the peritoneal cavity of rats whose drinking water contained arsenic. Embryonal cells are especially sensitive to arsenic which provoked in them signs of degeneration even in concentrations of 0.25 μg/l. of cultivation medium (*34*). Repeated, long-term treatment of the skin of white mice with an 18% solution of sodium arsenate induces squamous cell carcinoma. With oral administration, this phenomenon is not observed (35).

The results of the experiments do not seem to be a simple confirmation of clinical experience, especially when we consider the carcinomas of internal organs after arsenic exposure. It should be stated however that in view of the very long latency of arsenical carcinomas observed clinically, the animal experiments were hardly comparable. It was found that arsenic causes fragmentation and reconstruction of chromosomes during mitosis, thus causing either mutation or cell death. This "colchicine-type" effect is the mechanism on which arsenic treatment of hemoblastosis was based. Clinical experience argued for the possibility that arsenic works as a carcinogen primarily in pathologically altered terrain—skin hyperkeraroses, cirrhotic liver, (vineyards) chronic bronchitis from industrial irritants, and so on. Nevertheless, activation analysis of epitheliomas has shown smaller quantities of arsenic in the epitheliomas themselves than in the neighboring healthy skin (*36*). It is well known, however, that substances with delayed effects, e.g., beryllium, are not present in the affected tissue in important quantities at the time pathological changes manifest themselves.

Teratogenic effects have been ascribed to arsenic as well. Its teratogenicity was demonstrated in golden hamsters (*37, 38*), in mice (*39*), and in rats (*40*). The four most frequently seen soft tissue malformations were eye defects (anophtalmia and microphtalmia), exencephaly, renal and godonal ageneses. Ribs and vertebrae were the skeletal elements most susceptible to arsenic treatment. When introduced into fertilized bird eggs, arsenic causes beak and brain malformations (*41*).

At the end of chronic exposure of mice to arsenic in drinking water (50 ppm), we found the germinal epithelium of the testes considerably damaged (*42*). Possible genetic risks from arsenic exposure have been indicated in experiments which demonstrated the ability of inorganic arsenicals to provoke chromosomal aberrations in human lymphocytes *in vitro* (*43, 44*). Cell division defects and increased frequency of chromosomal abnormalities were found in patients treated with arsenic-containing drugs over long periods of time (*45*). Arsenic in combination with the referential mutagen [chemosterilant TEPA, tris (1-aziridinyl) phosphine oxide] provoked a significant increase in dominant lethal mutations in mice of the F_3 generation. The probable explanation of this phenomenon, observed only at higher exposure rates, is that arsenic damages the natural mechanism of chromosome repair, e.g., by blocking SH groups which play an important role in enzymes involved in such repair (*46*).

Several studies performed heretofore demonstrate also nonoccupational environmental as well as occupational exposure of populations of different regions to arsenic (*28, 29, 47–50*). In view of this fact, it seems reasonable to continue thoroughly organized epidemiological studies in regions of excessive arsenic exposure to study the question of the carcinogenicity of this substance. To obtain comparable results it may be useful to standardize the epidemiological approach to this problem on an international basis, which would be a task for WHO.

The inconclusive results of past experiments in arsenic carcinogenicity certainly do not justify cur-

tailing this research. New approaches, such as perhaps the combination of arsenic with other known or suspected carcinogens, may be of value.

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