THE TOXICOLOGY OF ARSENIC: CARCINOGENIC EFFECTS

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A B S T R A C T

Suspicion that exposure to arsenic may increase the incidence of cancer date from 1820, then referred to as carcinoma of the scrotum in copper smelters. Much of the efforts since then have produced questionable results in experimental studies using animals. Epidemiologic evidence has continued to implicate arsenic in human carcinogenesis. New evidence revealed clear dose-response relationship of the cancers to arsenic, making it unlikely that exposure to another agent may be the etiologic factor. Failure to reproduce arsenic cancers experimentally is puzzling. Perhaps species' specific differences play a role; the real carcinogen involved in these cases is not arsenic *per se* but a closely adhering contaminant. Definitive studies are needed to clarify this question.

The history of cancer observations are given in Table I. It all began in the 1820's and was attributed to a man named Dr. Paris who had observed cancer of the throat in copper smelters. Interestingly, in 1879, another group of investigators had noted cancer of the lung among uranium miners in Joachimsthal. This was some 16 or 20 years before the discovery of radioactivity and its biological effects were known. This was put into proper perspective, and it is believed that this was one of the findings which served to discredit arsenic as a carcinogen in the minds of most people.

Some of the other evidence which incriminated arsenic as a carcinogen was also flimsy. Cases of veterinary observations with deer and sheep in the 1930's also are listed in Table I.[1-2] Human evidence was not accumulated until after World War II. Both in England, where the main exposed population was sheep dip workers, and in Germany, where the main exposed population was vineyard workers, cases of arsenic carcinogenesis were suspected, and in some cases "proven". (It is uncertain to what degree we can use this word.) Lee and Fraumeni[3] conducted a classic study (to which references often are made these days) showing the excess of lung cancers in arsenic smelter workers. This is believed to be the first study which showed a clear-cut dose and effect relation between arsenic exposure and incidence of this cancer.

Another study of equal importance was published just a few months ago by a group from the Dow Chemical Company.[4] This study showed excess lung cancer, also dose related, among calcium and lead arsenate workers.

In this case, dose "relatedness" seems to be the real feature used to incriminate arsenic as the etiologic agent.

TABLE I

ARSENIC CANCERS

1820 Paris	Cancer of the larynx in copper smelters
1879 Harting & Hesse	Cancer of the lung in Joachimsthal
1937 Prell	Skin cancer in deer living downwind from As smelter
1939 Nieberle	Adenocarcinoma of the nasal sinuses in sheep
1948 Hill & Faning	Excess skin & lung cancer among sheep dip workers
1957 Roth	Lung, skin, liver, esophagus & bile duct cancers among Moselle
1969 Lee & Fraumeni	Excess lung cancers, dose-related, in As smelters
1974 Ott, Holder & Gordon	Excess lung cancers among Ca & Pb arsenate workers

Adapted from Prell, H., Arch Gewerbepathol Gewerbehyg and Nieberle, H., Z Krebsforsch

Obviously, as already pointed out, the proof of the pudding is the production of arsenic cancer under experimental conditions, which Table II summarizes. There have really been a frustrating set of data, as we all know. It all goes back to the 1920's again and you can see what kind of experiment was done in those days. In an experiment where about 2/3 of the animals die of arsenic poisoning of a nonneoplastic nature, few conclusions can be made as to what happens to the survivors. Indeed only one of a hundred survivors had two papillomas.[5] Indeed, that is weak carcinogenic evidence. The same experiment repeated a second time produced no malignant results.

In another study in 1942,[6] arsenic metal was implanted in the femur bone. We all know the significance of this and we know what trauma does to carcinogenesis. In this particular case no adequate controls were used. So, this also cannot be accepted as evidence. In Heuper's studies from 1942 on,[7] and in essence, according to the admission of the

author, there has been no positive demonstration that arsenic was carcinogenic under experimental conditions.

TABLE II

EXPERIMENTAL ARSENIC CANCERS

Leitsch 1922:	As_2O_3 in EtOH--paint on mouse skin
	67% died of As poisoning
	one of 100 survivors bore 2 papillomas
Leitsch 1923:	Repeat - negative results
Schinz 1942:	As metal implanted in femur bone of 4 rabbits
	1 developed sarcoma, no controls
Heuper 1942:	10 congenitally hairless rats fed $As(OH)_3$
	1 papilloma, no controls
Heuper 1954:	negative results on painting, feeding, injection

Table III shows some of the later data of Heuper and Payne.[8] This is a good example of the kind of "positive" evidence that one has to work with in order to claim that arsenic is carcinogenic in experimental animals. One can see that the controls had an incidence not significantly different from what the arsenic-dosed animals had.

TABLE III

DEATH DISTRIBUTION AND TUMOR YIELD IN RATS AND MICE
GIVEN ARSENIOUS OXIDE AND ETHYL ALCOHOL IN THEIR DRINKING WATER

TREATMENT	SPECIES	Months							Sites and Number of Cancers				
		0-6	7-0	10-12	13-15	16-18	19-21	22-24	PLEURA	LIVER	LYMPH NODE	UTERUS	SKIN
Arsenic + Alcohol Set I	Rats	1	3	3	5	10	12	16	3	2	4	2	2
	Mice	25	25	-	-	-	-	-	-	-	-	-	-
Arsenic ± Water Set II	Rats	4	2	2	2	5	2	32	2	1	2	-	-
	Mice	8	2	12	16	6	3	3	-	-	-	-	-
Alcohol Set III	Rats	6	1	4	4	7	13	15	3	2	1	-	-
	Mice	13	33	4	-	-	-	-	-	-	-		-
Water Set IV	Rats	0	0	2	1	9	10	28	1	5	2	-	1
	Mice	7	10	11	11	9	2	-	-	-	-	-	-

**Adapted from Hueper, W. C. and Payne, W. W., Arch Environ Hlth*

The new data, shown in Figure 1, are taken from the recent paper by Ott, Holder, and Gordon.[4] This, of course, is impressive because you would expect this kind of exposure if arsenic was the etiologic agent. However, it should be emphasized that this evidence is from an epidemiologic study; and no epidemiologic study could possibly identify with certainty an etiologic agent, because in a practical situation people are always exposed to a mixture of things. Also, it is always possible that there is a closely adhering contaminant, such as selenium or something else.

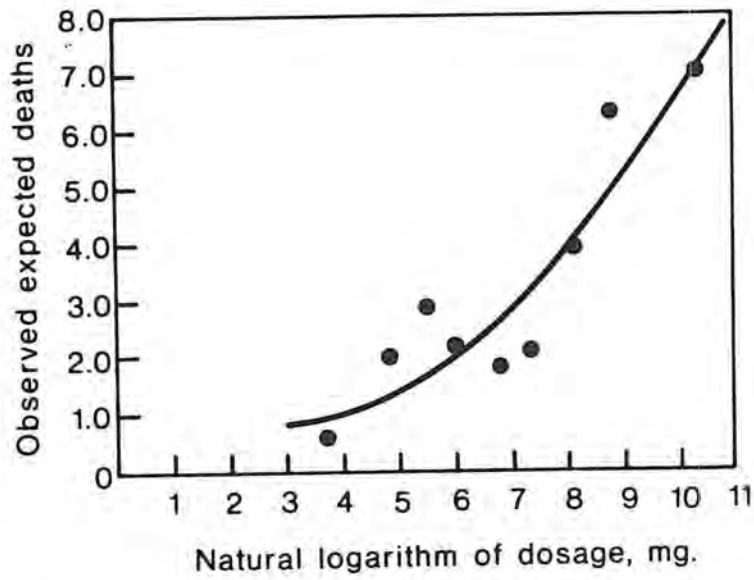

Figure 1 Ratio of observed to expected respiratory cancer deaths by dosage

Adapted from Ott, Holder, & Gordon, 1974

Epidemiologic evidence alone can only show a higher incidence of a certain disease in a certain population, but to attribute it to any one thing is extremely difficult. This is why experimental carcinogenesis work is so important in pinning down the etiologic agent. This, however, has not been done with arsenic. Some people believe that it is a "species specific thing" and that maybe the lower animals metabolize arsenic differently from humans. It is uncertain that this is accurate if it can be so, because there is no other evidence regarding this.

β-naphthylamine is regarded as unsuccessful as an experimental bladder carcinogen in all lower animals, but there are primates which

can perhaps be used and maybe such an experiment should be done. More arsenic carcinogenesis work needs to be done, which means research, more federal funding, and more report writing. Some ingenious novelists of the last decade or so had already anticipated this.*

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**The speaker concluded his presentation by projecting the title page of E. G. Loves' novel, "Arsenic and Red Tape."*

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