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Malignancies Due to Occupational Exposure to Benzene

Muzaffer Aksoy, MD

There is no doubt about the leukemogenic effect of benzene in man. The evidence is as follows: (1) The incidence of leukemia in shoeworkers exposed to benzene in a period of 8 years in Istanbul was 13.6/100,000, which is significantly higher than that for leukemia in the general population. (2) Following the phase-out of benzene in Istanbul, the number of leukemic workers decreased and none were reported in the subsequent 3 years. (3) The development of leukemia in pancytopenic patients with benzene exposure was observed in 13 out of 51 patients. (4) The differences in the distribution of the types of leukemia in individuals exposed and in nonexposed groups were as follows: acute leukemia %.1% in the former group, and 46% in the latter group. The high percentages of acute erythroleukemia and preleukemia were other interesting findings in the exposed group. (5) Two cases of leukemia were observed in a 6-year period at a tire cord manufacturing plant with 550 workers. At one location in the plant the concentration of benzene measured by gas chromatography was nearly 110 ppm. Additionally, we have studied 12 cases of malignant lymphoma, four cases of multiple myeloma, and six cases of lung cancer, all of whom were chronically exposed to benzene. The possible role of benzene in the etiology of these malignancies is discussed.

Key words: chronic benzene exposure, metabolic detoxification, occupational exposure, pancytopenia, preleukemia, shoeworkers, tire manufacturing

INTRODUCTION

Following the first description of a possible case of leukemia by Le Noire [1897] and the later description of a second patient with acute lymphoblastic leukemia due to occupational exposure to benzene by Delorc and Borgamano [1928], different types of hematopoietic malignancies such as malignant lymphoma, multiple myeloma, paroxysmal nocturnal hemoglobinuria (PNH) and myeloid metaplasia, associated with the use of this chemical, have been reported [Aksoy, 1980, 1981, 19821. Recently we have suggested that benzene might also cause lung cancer [Aksoy, 1980, 19811.

The purpose of this paper is to summarize and to discuss the malignancies due to chronic benzene exposure.

TUBITAK, Research Institute for Basic Sciences, Department of Biology P.K. 74, Gebze, Kocaeli, Turkey.
Address reprint requests to Professor Muzaffer Aksoy, M.D.. Istanbul Tip Fakultesi, Ic Hastaliklari Anabilim Dali. Hematoloji Bilim Dali. Capa-Istanbul, Turkey
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MATERIALS AND METHODS

During the period of 1967-1983, we studied a total of 73 patients. all chronically exposed to benzene. of which 51 had leukemia, 12 had malignant lymphoma, four had multiple myeloma. and six had lung cancer'. Sixty-two of them were examined at the Hematology Section, Istanbul Medical School. The remaining 11 subjects (ten with acute leukemia and one with multiple myeloma) were studied in the hematology departments of the Istanbul and Cerrahpasa Medical Schools and the Istanbul Social Insurance Hospital. Sixty-six of these patients have previously been described [Aksoy, 1980, 1981, 19821. Forty-eight cases occurred among a group of 28,500 shoeworkers who were chronically exposed to benzene [Ahoy. 1980, 1981, 1982]. The remaining 25 patients were employed at different facilities, such as print shops, furniture manufacturng workshops, and painters workshops. The working conditions and measurements of benzene in the working environment and in the adhesive solvents used were described elsewhere (Aksoy and Erdem. 1978; Baslo and Aksoy, 19821.

RESULTS AND COMMENTS

Leukemia

Following epidemiological studies in Istanbul and later those of Infante et al [1977], today there is no doubt that benzene is leukemogenic in man (Aksoy et al, 1974a; Aksoy and Erdem, 1978]. Evidences showing the leukemogenic effect of benzene in human beings can be summarized as follows.

Incidence of **leukemia in shoeworkers exposed chronically to benzene in Istanbul.** An epidemiological study among 28.500 shoe-, slipper-, and handbag-workers in Istanbul was performed during the period of 1967–1974 [Aksoy et al; 1974a, 1976a; Aksoy, 1980, 1981. 1982). During this period. 34 leukemic individuals were detected among this group of workers'. The crude incidence of leukemia in these workers was 13.59 per 100,000, which is significantly higher than the incidence of 6 per 100,000 in the general population [Aksoy et al. 1974a, 1976a]. However, the incidence of leukemia among the general population in Turkey according to the official health statistics yearbook of Turkey is between 2.25 and 2.80 per 100,000 [Aksoy, 19771.

Decline of **leukemia after phaseout of benzene in Istanbul.** As can be Seen in Table I, the peak incidence of leukemia among shoeworkers in Istanbul occurred in 1973 [Aksoy et al., 1976a; Aksoy, 1980, 19821. The number of new leukemic shoeworkers decreased in 1974-1975 to the level of 1969-70 and none were reported in the subsequent 3 years. But between 1979 and 1983, we have observed 11 new cases of acute leukemia and one of chronic myeloid leukemia associated with chronic exposure to benzene. Only one of these 11 new leukemic patients was a shoeworker living in Istanbul. Thus the number of leukemic individuals associated with chronic exposure to benzene increased from 34 in 1967–1974 to 51 in 1983. The decline in

[1]During this period, two cases of PNH (Puroxysmal nocturnal hemoglobinaria) and three cases of myeloid metaplasia associated with chronic exposure to benzene were also diagnosed.

[2]Three leukemic individuals were not included in the study due to the profession in two. OM being a furniture worker and the second working in a printing shop. The third individual was not included because his working place was not in Istanbul.

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TABLE 1. Annual Number of Leukemic Shoeworkers in Istanbul Between 1967 and 1978

Years	No. Leukemic shoeworkers
1967	1
1968	1
1969	3
1970	4
1971	6
1972	5
1973	7
1974	4
1975	3
1976	0
1977	0
1978	0

TABLE II. Preceding Pancytopenic Period in 51 Leukemic Patients With Chronic Exposure to Benzene

Types of leukemia	Total No. of leukemic patients	No. leukemic patients with preceding pancytopenic period
AML	20	5
Preleukemia	7	4
Acute Erythroleukemia	10	2
Acute Myelomonocytic	5	1
Acute Undifferentiated	1	1

the annual Occurrence of leukemia in the series of shoeworkers in Istanbul may be attributed to the gradual prohibition and discontinuation of the use of benzene in this city starting in 1969 [Ahoy, 1980, 1981, 1982]. On the other hand. the reappearance of leukemia after 1979 in Istanbul and other cities may be attributed either to the variation of the interval between the occurrence of leukemia and exposure or to the use of solutions containing benzene.

The development of leukemia in pancytopenic patients exposed chronically to benzene. In our series, a preceding pancytopenic period was present in 13 out of 51 patients (25.5%) (Table II). The interval between the onset of the preceding pancytopenic period and that of leukemia varied from 6 months to 6 years. In three patients with preleukemia and acute myeloblastic leukemia (AML), it was 6, 4 and 3 years, respectively. On the other hand, in a follow-up study of 2-17 years on 44 pancytopenic patients with chronic exposure to benzene, leukemia developed in six (13.6%) and fatal myeloid metaplasia in one (2.8%) [Aksoy and Erdem, 1978].

Difference in the distribution of the types of leukemia found in individuals chronically **exposed to benzene and in nonexposed patients.** As can be seen from Table III, there was a striking difference relating to the distribution of the types of leukemia in exposed and nonexposed leukemic patients. These differences *can* be summarized as follows: (1)While the percentage of acute leukemia was 96.1% in the exposed group, it was *46%* in the nonexposed group. In another study consisting of 696 patients performed in the Hematology Section of Istanbul Medical School, during a period of 10 years, 3% had acute leukemia (57%) and 299 had chronic leukemia

TABLE III. Comparison of the Types of Leukemia in 51 Individuals With Chronic Benzene-Exposure and 50 Nonexposed Patients

Type of leukemia	Patients Exposed[1]		Patients Nonexposed[1]	
	No.	%	No.	%
AML	20	39.25	8	16
ALL	5	9.80	13	26
Preleukemia	7	13.75	2	4
Acute Erythroleukemia	10	19.60	1	2
Acute Myelomonocytic	4	7.85	2	4
Acute Monocytic	1	1.95	1	2
Acute Undifferentiated	1	1.95	0	0
Acute Promyelocytic	1	1.95	0	0
CML	2	3.90	10	20
CLL	0	0	13	26

[1]Average ages of 50 nonexposed leukemic individuals who have been studied in our clinic and those of 51 of the leukemic patients with chronic benzene exposure were similar: 37.7 and 37.8 years, respectively.

(43%) [Aksoy et al, 1984b]. (2) The nonexposed group showed CLL in 26%. while none from the exposed group exhibited this form of leukemia. (3). The high frequency of acute erythroleukemia and preleukemia[3] is a very striking feature of the exposed group [Aksoy et al. 1976a; Aksoy. 19821. The average age of leukemic patients with chronic exposure to benzene was 37.8 years and the average duration of exposure was 9.93 years.

Occurrence of two cases **of acute leukemia in 6-year period in a tire cord manufacturing plant.** In a very modem tire cord manufacturing plant established 6 years ago near Izmit, a city very close to Istanbul, two *cases* of acute leukemia, one myeloblastic and the second lymphoblastic, were recorded. In this plant, approximately *550* workers were employed yearly. The working conditions were usually good and workplaces were large and properly ventilated. The concentration of benzene measured by a gas chromatography (Varian) in one place of the plant was 110 ppm. and in one of the solvents used in the auxiliary repair shop the benzene content was nearly *5%* [Ozeris et al, 19841. Thus, the incidence of leukemia was 60.6 per 100,000 in *550* workers in a period of 6 years.

Cholera Vaccination

Cholera vaccination is a contributory factor or promoter in the development of leukemia due to benzene exposure. As *can* be seen from Table I, which shows the annual number of leukemic shoeworkers in Istanbul in the period of 1967–1974, the peak incidence of leukemia due to chronic exposure to benzene was in 1973. Furthermore, there was a marked increase in the annual number of the patients with acute leukemia associated with benzene exposure since 1971. Although there were nine leukemic patients in the 4-year period (1967–1970), this number subsequently increased to 22 in 197
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[3]The term preleukemia is used for any *hematologic* syndrome that may in time develop into oven leukemia but which lacks the criteria essential for the diagnosis of overt leukemia when the patient is first seen. Our criteria for diagnosis of preleukemia were similar to those of Wintrobe et al [1981]: (1) The presence of refractory anemia. mostly hypochronic and often associated with thrombocytopenia or pancytopenia; (2) normal ranging or slightly increased percentages of myeloblasts in the bone marrow; and (3) the presence of few blast cells, mostly myelobiasts, in the peripheral blood film.

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Patients Nonexposed[a]	
No.	%
8	16
13	26
2	4
1	2
2	4
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0	0
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10	20
13	26

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creased to 22 in 1971–1974. This sudden increase of leukemia after 1970 in shoeworkers studied has led us to look for additional factors besides this chemical agent. With the appearance of some cholera cases in Istanbul at the beginning of September 1970, the majority of the population in Istanbul was vaccinated against this infectious disease. The cholera vaccination was performed in 14 of our leukemic patients associated with chronic exposure to benzene. However, we were not able to find out whether the remaining eight patients were Vaccinated against cholera or not, because during our study this possibility was taken into consideration only after 1973. On the other hand, a variety of postvaccinal reactions are well-known, such as the activation of inactive tuberculosis. Therefore, in our cases of leukemia with chronic exposure to benzene, hypothetically, immunization to cholera may have played a contributory role, possibly as a promoting agent, in the development of leukemia, in addition to chronic exposure to benzene. A study performed by Lenz and Pluznik [1982] showed that clonal growth of murine granulocyte/macrophage progenitor cells (CFU_c) was inhibited by cholera toxin in soft agar cultures. This problem needs further study, particularly in animals.

Familial Connection and Individual Susceptibility

In five leukemic patients with chronic exposure to benzene in our series a familial connection was established [Aksoy et al., 1974b, 1976a, b; Aksoy, 19821: two were uncle and nephew and two were cousins. The father of the fifth leukemic patient, a 65-year-old shoeworker with a long history of exposure, died in a hospital with the diagnosis of myelosclerosis, but re-evaluation of the case-report showed that this patient possibly had acute leukemia of an unidentified type. These five leukemic patients among first- and second-degree relatives constituted 9.8% of leukemic patients with benzene exposure. In these five patients, the development of leukemia was possibly due to the presence of intrinsic factors in addition to benzene as an environmental factor. This suggestion is in accordance with the view that leukemia may be due to the combination of various intrinsic and extrinsic factors [Gunz, 1970; Aksoy et al, 1974b; 1976b; Aksoy, 1982]. Furthermore. individual or family susceptibility as suggested by Reifschneider [1965] has been considered as one of the main factors in the incidence of chronic benzene poisoning Browning. 1965]. There are several studies in favor of great variation in individual susceptibility [Rejsek and Rejokova, 1956; Savilahti, 1956; Aksoy et al. 1974b]. As a very illustrative example of individual susceptibility. we should like to present here a family associated with chronic exposure to benzene. The husband, 38 years old, and his wife, 32 years old, were engaged in a job of manufacturing whistles. For this purpose, they dipped plastic material into an open vessel of benzene solution containing 88.42% benzene and 9.25% toluene as determined by gas chromatography. Following an exposure to benzene for a period of 6 months, severe aplastic anemia developed in the wife [Baslo and Aksoy, 1982]. In contrast, following an exposure of 14 years, all hematologic data for her husband were within normal limits. The cause of this variation concerning individual susceptibility is not completely understood. According to Browning, the most probable explanation lies in innate differences in the capability of different individuals to carry out the metabolic detoxification [Browning, 1965].

Malignant Lymphoma

Some investigators published a few case reports showing the possible role of chronic exposure to benzene in lymphosarcoma and reticulosarcoma [Bousser et al,

1947; Paterni and Sarnari, 1968; Casirola and Santagari, 19691. In 1974, the present author and his associates described six cases of Hodgkin's disease associated with chronic exposure to this chemical among a series of 94 patients with this type of malignant lymphoma [Aksoy et al, 1974c]. Despite the lack of statistical data, we suggested that chronic exposure to benzene might play a role in the development of Hodgkin's disease. Since that time, we have studied six other cases: one case of histiocytic lymphoma, two of lymphocytic lymphoma, and three of Hodgkin's disease. All were chronically exposed to benzene for 10–17 years. In 1979, Vianna and Polan performed a comparative study on the 1950–1969 mortality rates for reticulum cell sarcoma, lymphosarcoma, and Hodgkin's disease among male workers aged 20 years or older in different occupations with chronic exposure to benzene or other coal tar fractions and among a nonexposed control group. The relative risks were calculated for the different occupations based on crude death rates: for seven occupations for which age distributions were available (80% of the male population studied), age-specific death rates for each lymphoma type were calculated and applied to the age distribution. The relative risks in the exposed group were 1.6, 2.1, and 1.6 for reticulum cell sarcoma, lymphoma, and Hodgkin's disease, respectively. Furthermore the increase in the risk seems to be limited to those aged 45 years and over at death, an observation which is consistent with the possibility that chronic exposure to benzene and/or other coal derivates might be important in the etiology of this kind of tumor. In addition, there are some studies showing a high rate of mortality from malignant lymphoma among pathologists, chemists, and persons who handled chemicals containing benzene [Olsson and Brandt, 19791.

Multiple Myeloma

In 1970 Torres et al described two patients with IgG myeloma with chronic exposure to benzene. In the last 10 years, we have studied four patients with multiple myeloma possibly due to chronic exposure to benzene. The first was a 63-year-old shoemaker: the second was a 36-year-old technician in an airplane repair plant who had the Bence-Jones type of multiple myeloma; the third was a 59-year-old manager in a plastic plant who showed the IgG type of this hematologic malignancy: and the fourth was a 58-year-old owner of a furniture-manufacturing shop who had the IgA type of multiple myeloma [Aksoy, 1980, 1981; Aksoy et al, 1984a]. All had been exposed chronically to benzene for a period varying between 7 and 35 years (mean: 18 years). In agreement with the observation of Torres et al [1970], our findings of multiple myeloma associated with chronic exposure to benzene indicate that benzene may be an etiologic factor in the development of multiple myeloma. Recently. Decouflé et al [1983] performed a historical cohort mortality study consisting of 259 employees of a chemical plant where benzene has been used in large quantities. According to these investigators, the findings are consistent with previous reports of leukemia following occupational exposure to benzene, and they raise the possibility that multiple myeloma could be linked to benzene also.

Lung Cancer

Considering the occurrence of six cases of lung cancer among the individuals associated with occupational exposure to benzene, the present author suggested a causal relationship between this chemical and lung cancer [Aksoy, 1980, 19811. In these cases duration of exposure ranged between 8 and 35 years (mean: 17 years).

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Only three of these cases had mild hematologic abnormalities such as leucopenia or lymphopenia. In two patients, the histopathological diagnosis was oat-cell carcinoma. In addition to this, all patients were heavy or moderate smokers. Because benzene available in Turkey did not contain benzo(a)pyrene determined by ultraviolet spectrophotometry [Aksoy and Erdem, 1978], lung cancer in these individuals cannot be attributed directly to this carcinogenic agent present in benzene. Benzene is mainly absorbed via the lungs and about 40% of the absorbed portion is exhaled unchanged; after 24 hours a small percentage of benzene can still be detected in the expired air [Sherwood and Carter, 1970]. Therefore, a carcinogenic effect of benzene in the lungs is possible. Because our patients were also smokers, a possible role of smoking in the development of lung cancer should also be considered.

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Peter F. Infante, DDS, r

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