BENZENE AND MALIGNANCIES

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During the period between 1967 and 1990, 90 patients were studied who had different types of malignancies including 59 leukemias, 13 lymphomas, 5 multiple myelomas, 8 lung cancers, 3 myeloid metaplasias, and 2 paroxysmal nocturnal hemoglobinuria. The incidence of leukemia in shoeworkers exposed chronically to benzene in a period of eight years in Istanbul was 13.6/100,000, which is significantly higher than that for leukemia in the general population. Following the phase-out of benzene in Istanbul, the number of leukemic workers decreased and none were reponed in three years. The development of leukemia in pancytopenic patients with chronic benzene exposure was observed in 14 out of 59 individuals. Also studied were 13 malignant lymphoma, 5 multiple myeloma, 8 lung cancers, and 2 paroxysmal nocturnal hemoglobinuria. The role of benzene in t k etiology of these malignancies is discussed.

The relationship between diseuses and occupations was established by Ramazzini in the 17th century. Despite this long-standing knowledge, the clinical discipline of occupational medicine was initiated only recently. Among numerous chemicals, benzene is the only one which causes severe hematologic diseases. Benzene is the parent "hydrocarbone" of the aromatic group of chemicals which stems not only from industrial sources but also is present in natural products. Incomplete combustion of natural products causes the formation of benzene. Tobacco smoke also contains tract amounts of benzene. According to Wallace (1989), smokers have breath concentration of benzene around 14 $\mu g/m^3$, while for non-smokers the range is around 2$\mu g/m^3$. Benzene u absorbed via the lungs and approximately 40 or 50% of it is retained in the organs according to the amount of their lipid contents. The major organ systems implicated for benzene metabolism are t k liver and bone marrow, in cytochrome P-450. The mixed function oxidases in the endoplasmic reticulum of the parenchyma cells of the liver perform epoxidation of the nucleus to form arene oxide which decomposes to phenol and otkr metabolites.

Recently it was shown experimentally in Sprague-Dawley rats, Wister rats, and Swiss mice, that high doses of benzene cause a rapid decrease

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of colony forming cells (CFC) and toxic alteration of the somatic cells of the microenvironment. Any agent toxic to pluripotent stem cells can cause an alteration in two important capabilities of the CFCs (Dexter et al., 1985): 1). A block or disturbance in self-renewal will cause aplastic anemia. 2). A block in the long-term differentiation to produce a variety of lineage restricted progenitor cells will cause leukemia.

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

MATERIAL AND METHODS

During the period from 1967 to 1990 a total of 90 patients with malignancies due to benzene toxicity were studied. Fifty-nine had leukemia. 13 malignant lymphoma. 5 multiple myeloma. 3 myeloid metaplasia. 8 lung cancer and 2 had paroxysmal nocturnal hemoglobinuria. Also studied were 109 cases of aplastic anemia resulting from chronic benzene exposure. Most of the patients were shoeworkers, but some were employed at other jobs such as print shops and railway repairplaces. Two were dyers and two were physicians in hormone and biochemistry laboratories. The content of benzene in adhesives and thinners used in these occupations was determined by gas chromatography and ranged between 8 and 88%. Hematological methods were standard.

RESULTS AND COMMENTS

Following the epidemiological studies performed in Istanbul (Aksoy et al., 1974). in Milan and Pavia (Vigliani and Forni, 1976), in the US. (Infante et al., 1977; Rinsky et al., 1981). and in China (Yin et al., 1987), it is impossible to suspect the validity of the fact that benzene is a potent carcinogenic agent in humans. The facts supporting this assumption are the detailed below.

The Incidence of Leukemia Among Shoe, Slipper, and Handbag Workers Exposed Chronically to Benzene in Istanbul

The use of benzene-containing glue-adhesives in Istanbul started approximately between 1955 and 1960. Shoes, slippers, and handbags were manufactured mostly in small and unsanitary workshops. Following the appearance of benzene-containing adhesives in the market, the shoeworkers replaced their old adhesives with the new one (Aksoy, 1977, 1988). Since 1961 numerous cases of chronic benzene toxicity such as leucopenia thrombocytopenia, and pancytopenia have been noted in Istanbul. In 1968 and 1969 a hematological study was performed among 217 apparently healthy workers with chronic benzene exposure. Of these individuals 23.5% disclosed hematological abnormalities such as leucopenia, thrombocytopenia, and pancytopenia (Aksoy et al., 1971). In 1960 to 1972, 46 cases of benzene-mediated aplastic anemia were investigated (Aksoy et al., 1972). Among them, 34 were from small shoe-manufacturing workshops where benzene-containing material was used. In addition, the benzene content of

88 adhesives and thinners available between 1970 and 1972 in Istanbul ranged between 8 and 88% (Topuzoglu, 1972). Tanguin *et al.* (1967) described six shoeworkers with severe *aplastic* anemia due to chronic *exposure* to benzene *in* Istanbul. During this period 31 leukemic individuals were found among the group mentioned The crude incidence of leukemia in these shoeworkers was 1359 per 100,000 (Aksoy et al., 1974a). The peak incidence of leukemia among the workers described above was recorded in 1973, and it was 24.5 per 100,000.

Decline of Leukemia Following Phase-out of the Use of Benzene in Istanbul
The annual number of leukemic shoeworkers with chronic benzene toxicity started *to* decrease following the prohibition and gradual discontinuation of the use of benzene containing adhesives.

The occurrence of two cases of acute leukemia in a six year period in a tire cord factory. In 1984 two cases of acute leukemia were investigated, one myeloblastic and the second lymphoblastic. in a modern tire *cord* factory in Izmit, a city very dose to Istanbul (Aksoy et al., 1987). Approximately 550 workers were employed yearly in this plant where working conditions were usually good and workplaces were large and properly ventilated. Despite the good conditions, at one location the concentrations of benzene determined by *gas* chromatography (Varian) at one location in the plant was 110 ppm and the solvents used in the auxiliary repair shop were nearly 5% benzene (Aksoy *et* al., 1987). Thus the incidence of leukemia was 60.6 per 100,000 in 550 workers in a six year period.

Development of Leukemia in Pancytopenic Patients
In *our* study comprising 59 leukemic workers with chronic benzene toxicity a preceding pancytopenic period was present in 14 patients, which is 23.7%. In addition, in a case with aplastic anemia with *chronic* benzene toxicity. myeloid metaplasia developed following a seven year complete recovery period.

Individual Susceptibility and Genetic Factors
In *our* smdy of leukemia with chronic benzene toxicity in six patients. a familial connection was established: two uncles, a *nephew.* and two cousins. The father ofthe fifth leukemic shoeworker with benzene exposure died in a hospital in Istanbul with the diagnosis of acute myelosclerosis, but reevaluation of the *case* report showed that the patient with chronic exposure *to* benzene had an unidentified type of acute leukemia.

The sixth leukemic patient with chronic exposure to benzene had. like his son. *chronic* lymphoid leukemia. Although he was never exposed to benzene, he used a long-time saccharine and colchicine. The role of these two substances in the etiology of chronic lymphoid leukemia is unknown. These six leukemic patients among first and second generation relatives constituted 102% of the leukemic patients with chronic benzene exposure. In these *six* patients the development of leukemia was possibly due *to* the presence of genetic or intrinsic factors, in addition to the presence of environmental determinant. This suggestion is in accor-

dance with the view that leukemia may be due to the combination of various intrinsic and extrinsic factors (Gunz, 1970).

Individual Susceptibility

Individual or family susceptibility, as first suggested by Reifschneider (1922), has been considered as an important factor in the development of chronic benzene toxicity. There are numerous examples in favor of this assumption. For example, two of the β-thalassemic patients associated with aplastic anemia due to chronic benzene toxicity were brothers (Aksoy et al., 1975). Also, two pancytopenic patients with chronic benzene toxicity were cousins. The cause of the variation in the individual susceptibility observed in chronic benzene toxicity is obscure. According to Browning (1965), the most probable explanation lies in the innate difference in the ability of different patients to carry out the metabolic detoxification. Some individuals may be congenitally deficient in the capacity to detoxify benzene or its metabolites.

Insufficiency of Medical Supervision

One of the leukemic patients with acute erythroleukemia was a 23-year-old shoeworker with 11 years exposure, who was studied before the onset of his hematologic malignancy. He was one of the 217 apparently healthy workers with chronic exposure to benzene (Aksoy et al., 1971). At that time, his hematological data were within normal limits (RBC 4.6ml/mm^3, Hb 11.5g/100ml, hematocrit 45%, platelets 425,000/m^3, and WBC 4,600/mm^3 with normal differential counts). To our knowledge, in none of the 51 workers associated with hematologic abnormalities in the smdy of 217 apparently healthy workers with chronic exposure to benzene did leukemia later develop (Aksoy et al., 1971). In contrast to this, the aforementioned worker who was entirely normal in the previous smdy developed leukemia four years later. This case illustrates the inadequacy of medical supervision based solely on blood counts in individuals with chronic exposure to benzene.

Distribution of the Types of Leukemia in Chronic Benzene Toxicity

Interestingly, there are significant differences relating to the distribution of the types of leukemia associated with chronic benzene exposure. These are:

1. The difference in the benzene content. In cases of acute leukemia, the percentage of benzene concentration was high, ranging between 9 and 88%. On the other hand, benzene content of the material in patients with chronic lymphoid leukemia was as low as 2.8%.

2. Adhesives which were used by nearly all workers with acute leukemia in our study contained *only* benzene. In contrast, the adhesives used by the patients with chronic lymphoid leukemia also contained 95% toluene. Another patient with chronic lymphoid leukemia was lata exposed to different chemicals. And, the patient with hairy cell leukemia with chronic exposure to benzene later worked in a place where polystyrene and polyethylene were used

3. The great majority of the workers with acute leukemia in our study were exposed to high concentrations of benzene during working hours. Five out of six patients with chronic myeloid, two with chronic lymphoid, and one with hairy cell leukemia were exposed to benzene intermittently and for a short time during daily work. Considering these data, we suggested that the striking difference concerning the distribution of the types of leukemia in chronic benzene toxicity may be explained partly by exposure levels, the mode of exposure, and the presence or absence of other homologs of benzene such as toluene, xylene, and other chemicals.

Chronic Benzene Exposure, Malignant Lymphoma, Multiple Myeloma, and Lung Cancer

In 1960 Wirtschafter and Bichell showed that tissue responses could be observed in lymphnodes, spleen, thymus and bone marrow of rats *after* a single injection of benzene. Recently Irons et al. (1983) showed what the effect of benzene administration in mice on lymphocyte function is at doses of the compound that produce little or no measurable difference in the circulating cells. On the other hand, Aksoy published reports of six cases of Hodgkin's disease in which chronic benzene toxicity might play a role in the development of this malig*nancy*. Furthermore, we have *studied* seven more cases of different types of *malignant* lymphoma with benzene exposure.

Vienna and Polan (1979) performed a comparative study *on* the mortality rates of different types of malignant lymphoma among workers with chronic benzene exposure. Their results were consistent with the possibility that chronic exposure to benzene might be important in the etiology of malignant lymphoma. There are several studies showing a high mortality rate from different types of *malignant* lymphoma among pathologists, chemists, and persons who handled chemicals containing benzene.

Multiple Myeloma

In 1970 Torres et al. reported *two* cases of multiple myeloma associated with chronic benzene exposure. In 1980 Aksoy published reports of four *cases* of multiple myeloma associated with chronic benzene toxicity. In *one* of these cases there was a short paid of pancytopenia with hypoplastic bone marrow. In an epidemiological risk assessment study performed by Rinsky et al. (1981) there was a statistically significant increase in death from leukemia and multiple myeloma resulting from chronic benzene exposure

Lung Cancer

In 1976 a study by Aksoy, considering five individuals with lung *cancer* associated with chronic benzene toxicity, suggested that there is a causal relationship between this chemical agent and this malignancy. In our study of malignancies due to chronic benzene exposure there wen eight cases of lung cancer. The ages of these patients ranged from 31 to 57 years and the duration of exposure was between 8 and 35 years. In three patients, mild hematologic abnormalities such

as leucopenia or lymphopenia were established. Because benzene available in Turkey did not contain benzo(a)pyrene determined by ultraviolet spectrophotometry (Aksoy and Erdem, 1978), the lung cancer in these six patients cannot be attributed directly to this carcinogenic agent present. Benzene is absorbed mainly by the lungs and about 40% of this portion is exhaled unchanged. But after 24 hr a small percentage of benzene can still be detected in the expired air. Therefore, a carcinogenic effect of benzene, in addition to nicotine, is possible.

Recently in a case-control study in Shanghai, Levin et al. (1988) showed that there was a 70% of excess of lung cancer among workers in the chemical industry. These workers were likely to have been exposed to several chemicals such as bis(chloromethyl)ether and others. According to Levin et al. benzene was the most often mentioned when respondants specified exposures.

CONCLUSION

Benzene is the only chemical which causes hematologic abnormalities and malignancies. In addition, there is no safe level for this chemical. Therefore, benzene should be used only when there is no other possibility.

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