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Types of Leukemia in Chronic Benzene Poisoning. A Study in Thirty-Four Patients[1]

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Abstract. The distribution of various types of leukemia due to chronic exposure to benzene is described in a series comprising 34 cases. The incidence of leukemia among 31 shoe-workers was 13.5/100,000. Acute myeloblastic leukemia was the most frequent type, followed by preleukemia, acute erythroleukemia and acute lymphoblastic leukemia. The extreme rarity of chronic myeloid leukemia was a noteworthy finding. The differences and similarities between the distribution of various types of leukemia in different series of patients with chronic exposure to benzene and ionizing radiation are discussed.

The etiology of leukemia is still obscure. Despite this fact, the role of ionizing radiation and benzene in the development of leukemia is well-known [3–5, 8, 9, 11–17, 19]. During the period from 1967 to 1973, we collected 26 shoe-workers chronically exposed to benzene with acute leukemia in Istanbul and showed that the incidence of leukemia among them was 13/100,000 which is a marked and statistically significant increase over that of leukemia in the general population [3]. In addition, in 1974 we have observed 8 new individuals with leukemia associated with chronic benzene *poisoning*. The purpose of this paper is to report them and compare the types of leukemia in individuals chronically exposed to benzene and those exposed to ionizing radiations.

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Material and Methods

According to the official records there are 23,509 workers involved in the shoe, slipper and handbag industry in Istanbul [3]. The working conditions, including the mode of benzene exposure are described elsewhere [3, 6, 7]. In Istanbul, during the period from 1967 to 1974, 33 leukemic individuals chronically exposed to benzene[1] were found. With the exception of 2 (1 furniture-worker, 1 working in a printing shop), all were shoe-workers. Twenty-six of these patients were described elsewhere [3–5]. In 1974, 8 new leukemic patients with chronic exposure to benzene were studied in the Internal Clinic of Istanbul Medical School. The concentrations of benzene in their working environment measured by a Drager-Spurgerat-Multi Gas Detector Mod. 21 23, Lubek, were recorded to reach 210 or, rarely, 640 ppm when benzene-containing adhesives were used.

Results

Some clinical and hematological findings and the duration of exposure are given in tables I and II.

Types of leukemia. The comparison of the distribution of the types of leukemia found in these 34 individuals chronically exposed to benzene and those of 50 non-exposed leukemic patients is given in table III. Similarly, the ages of these non-exposed leukemic individuals who have been studied in our clinic during the last 1½ years varied between 16 and 60 years with a mean of 37.7 years. According to our results, acute myeloblastic leukemia seems to be the most frequent variety of this malignancy following exposure to benzene. Then comes preleukemia, erythroleukemia and acute lymphoblastic leukemia. The criteria for the diagnosis of preleukemia were similar to those of WINTROBE *et al.* [20]: (1) the presence of refractory anemia, mostly hypochromic or pancytopenia; (2) the percentages of myeloblasts in the bone marrow within the normal range or slightly increased, and (3) the presence of a few blast cells, mostly myeloblasts, in the peripheral blood film.

Pancytopenic period. A preceding pancytopenic period was present in 23.5% of all cases. It was noted in eight patients, three with acute myeloblastic leukemia, three with preleukemia, one with acute monocytic leukemia and one with acute erythroleukemia. Preceding pancytopenic period was particularly present in 50% of preleukemic patients. The interval between the onset of leukemia and that of pancytopenic period varied from 6 months to 6 years. It was the shortest in case 5 and the longest in

[1] One of the 34 leukemic patients was exposed to benzene outside of Istanbul.

Clinical, hematological and bone marrow findings in 8 new leukemic individuals through chronic exposure to benzene

	Cases							
	1	2	3	4	5	6	7	3
ars	36	53	13	41	21	45	28	36
n of exposure, years	7	20	1–2	4–12	5	8	1½	15
penic period	+	–	–	+	+	–	–	–
leukemia	AEL	AEL	ALL	PL	PL	CML	AML	AEL
logical findings								
C × $10^6/\mu l$	1.93	1.41	2.60	1.95	2.00	4.00	2.70	2.90
g%	3.9	3.5	7.3	5.4	4	10.1	8	7.8
C/μl	2,500	5,600	39,000	2,300	5,600	331,000	13,400	17,000
iculocytes, %	2.8	1	1	1.5	1	1	2.8	2.2
elets, × $10^3/\mu l$	10.0	15.0	10.0	115	10.0	300	90.0	22.0
matocrit, %	16	14	22	18	14	41	25	29
eloblasts, %	0	0	0	6	10	1	0	0
mphoblasts, %	0	0	60	0	0	0	0	0
elocytes, %	0	0	0	0	0	25	0	2
nocytes, %	3	2	1	0	2	0	91	3
cleated red blood cells/100 WBC	11	3	0	0	4	1	1	17
marrow findings								
eloblasts, %	12	40		5	21		4	5
nocytes, %	0	0		0	0		66	0
galoblasts, %	12	0		0	1		0	3
eloid series, %	35	43		69	46		13	25
ythroid series, %	55	43.5		2	33		14	58

EL = Acute erythroleukemia; ALL = acute lymphoblastic leukemia; PL = preleukemia; CML = chronic id leukemia; AML = acute monocytic leukemia; + = present; – = absent.
These findings were delivered by the bone marrow puncture performed in the preceding pancytopenic d. Two other bone marrow punctures performed during the leukemic phase yielded no material.

case 4, six months and six years respectively. Usually, the clinical and hematological findings of pancytopenia improved considerably or even disappeared completely. But despite this improvement, the findings of leukemia developed later, following a period of variable duration.

Incidence of leukemia during the period of 8 years, 31[3] patients with

[3] Three leukemic individuals were not included in the study due to the profession in 2, one being a furniture worker and the secocd working in a p:inting shop. The third individual was not included because his working place was outside of Istanbul.

myeloblastic leukemia	14	41.1	8	16
lymphoblastic leukemia	4	11.7	13	26
erythroleukemia	6	17.6	1	2
emia	6	17.6	2	4
monocytic leukemia	2	6.0	3	6
promyelocytic leukemia	1	3.0	0	0
: myeloid leukemia	1	3.0	10	20
: lymphoid leukemia	0	0.0	13	26

leukemia were observed among a group of 28,500 shoe-workers chronically exposed to benzene. Thus, there was an incidence of 13.5 per 100,000. This incidence was significantly greater ($p<0.001$) than the overall incidence of leukemia in the general population which was 6 per 100,000. The annual occurrence of leukemia among these shoe-workers is given in table IV. The peak of the occurrence of leukemia among this group was in 1973. In 1974, there was a decline in the number of carts. This decline of annual occurrence of leukemia may be attributed to the prohibition of the use of benzene since 1969.

Genetic factors. In three of 34 leukemic patients, the genetic predisposition was established. Two of them, a man and his paternal uncle had

Table IV. Annual number of leukemic shoe-workers in Istanbul between 1967 and 1974

Years	Number of leukemic shoe-workers	Years	Number of leukemic shoe-workers
1967	1	1971	6
1968	1	1972	5
1969	3	1373	7
1970	4	1974	4

acute leukemia, one lymphoblastic and the other myeloblastic. This family was described elsewhere [5]. The third patient, case 8 of the series presented here had acute erythroleukemia. His father, a 65-year-old shoeworker with a long history of benzene exposure died nearly 1 year ago in a hospital in Istanbul with the diagnosis of myelosclerosis. But re-evaluation of the case report showed that this patient possibly had an acute leukemia of unidentified type. The disease showed an acute course with severe gastrointestinal bleedings and profound anemia and there was no hepatosplenomegaly. Four sternal punctures yielded no material.

Some *contributary factors for the development of leukemia with a preceding* pancytopenic period. In 6 of 8 new patients with acute leukemia, corticosteroids were used during the course of pancytopenic period varying from some months to several years. In these pancytopenic patients, acute leukemia or preleukemia developed with an interval of 6 months to 6 years. In addition to that, re-exposure to benzene was also noted in 4 of these 6 patients.

Discussion

Since the first case report of leukemia due to chronic exposure to benzene appeared [17], numerous leukemic patients with chronic exposure to this chemical were described. As an example, BROWNING [9] collected 61 cases of leukemia with chronic benzene poisoning from the literature till 1965. More than that appeared in the literature since that time. The establishment of a marked and statistically significant increase in the incidence of leukemia among shoe-workers chronically exposed to benzene by this study and previous works [3] provided final evidence of the leukemogenic effect of benzene in man.

Types of leukemia. Thirty-three of 34 leukemic individuals of this series had various types of acute leukemia. Interestingly, there was only 1 case of chronic leukemia, myeloid *in* type. According to *this* study, acute myeloblastic leukemia seems to be the mort frequently encountered type of leukemia following chronic exposure to benzene. This finding is in accordance with those of VIGLIANI and SAITA [19]. In this study a striking increase in the number of the patients with preleukemia *(6* cases, 17.6%) and acute erythroleukemia *(6* patients, 17.6%) was noted. In this respect, with small differences, the frequency of various morphologic types of acute leukemia in our series was similar to that of GOGUEL *et al.* [13], obtained in 23 workers with acute leukemia due to chronic exposure to benzene. As noted above, in our series only 1 case of chronic myeloid leukemia was present. In contrast to our results, there are several reports describing the occurrence of chronic myeloid or even chronic lymphoid leukemia in the patients with chronic benzene poisoning. BROWNING [9] collected 21 cases of chronic myeloid and 6 cases of chronic lymphoid leukemia among *61* leukemic individuals with chronic benzene exposure. Furthermore, in 1967 GOGUEL et *al.* [13] noted that there were 16 cases with chronic myeloid and 8 with chronic lymphoid leukemia in their series *of* leukemic patients with exposure to this chemical. Therefore, it is difficult to explain the significant difference existing between the distribution of the types of leukemia due to chronic benzene poisoning established in our series and in the group arranged by BROWNING [9] and that of GOGUEL *et al.* [13]. On the other hand, if we compare the types of leukemia occurring in 34 exposed individuals and 50 non-exposed persons a striking difference can be seen between these two groups of leukemic patients. This result is in contrast to that observed among heavily irradiated survivors *in* Hiroshima and Nagasaki [8, 14–16]. The occurrence of chronic myeloid leukemia was frequent among these groups of survivors. Furthermore, a small but significant difference was found concerning the incidence of chronic myeloid leukemia *in* atomic bomb survivors in Hiroshima and Nagasaki, 33 and 18%, respectively [15]. This difference in the incidence rate *of* chronic myeloid leukemia was found to be related *to* the dose and the nature of the radiation [15]. On the other hand, the almost absence of chronic lymphoid leukemia among these groups of survivors of atonic bomb was explained by the infrequent occurrence of chronic lymphoid leukemia in Japan [16]. But in Turkish people, the distribution of the types of leukemia is almost similar to that observed in Western countries. Therefore, the absence of chronic lymphoid leukemia and the rarity of

chronic myeloid leukemia in our series is significantly [illegible]. On the other hand, our results are somewhat similar to those of COURT-BROWN and DOLL [11, 12] obtained in 50 patients receiving partial body irradiation for treatment of ankylosing spondylitis. In this study, 38 out of 50 cases had acute leukemia and only 8 patients with chronic forms, 7 myeloid and 1 lymphoid, have been found. According to this study, the data in the remaining cases were insufficient to determine the clinical type of this disease. Furthermore, there are numerous cases of leukemia following radio iodine treatment [1, 2, 10, 18]. With the exception of 2 examples of chronic myeloid leukemia [2, 18] all patients had acute leukemia.

The foregoing data show that the distribution of the types of leukemia following exposure to benzene varied significantly between studies [3, 9, 13, 19]. A certain relationship between the duration of exposure and the types of leukemia was noted in the present study (table II).

Finally, the role of genetic predisposition was evident in 3 of our leukemic patients in 2 families. In the first family described previously elsewhere [5], uncle and paternal nephew had acute leukemia, one lymphoblastic, the other myeloblastic. In the second family, the father had acute leukemia of unidentified type and his son had acute erythroleukemia. The occurrence of leukemia in these two families was more than a mere coincidence. Therefore, in our opinion, some genetic factors triggered by chronic exposure to benzene played a role in these two families with acute

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