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Followup Study on the Mortality and the Development of Leukemia in 44 Pancytopenic Patients With Chronic Exposure to Benzene

By Muzaffer **Aksoy** and Şakir **Erdem**

A followup study of 2–17 yr was performed on 44 pancytopenic patients with benzene exposure. They had been subjected to high concentrations of benzene (150–650 ppm) in adhesives for 4 mo to 15 yr. The benzene content of the adhesives varied between 9% and 88%, (average 50%). Complete remission was seen in 23 patients and fatal outcome due to complications of pancytopenia was observed in 14 pancytopenic patients. In 6 pancytopenic patients leukemia developed after a period of 6 mo to 6 years. In a patient with complete remission fatal myeloid metaplasia occurred. The mean age and the duration of exposure of 21 patients with overall fatal outcome were significantly higher than those of 23 patients with complete remission. However, with the exception of mean values of neutrophils, the findings in peripheral blood, including the levels of HbF and A$_2$ could not be correlated with the outcome of benzene-induced pancytopenia. On the other hand, in one patient a very low level of HbA$_2$ and a high level of HbF were already evident during the pancytopenic period, whereas preleukemio developed 9 mo later. This observation suggests that low levels of HbA$_2$ with or without high levels of HbF during pancytopenia may be a sign of leukemia. Moreover, there was a clear relationship between the type- of bone marrow cellularity and the outcome of pancytopenic patients. The development of leukemia in 6 of 44 pancytopenic patients with chronic exposure to benzene is further evidence for the leukemogenic effect of benzene in man.

ALTHOUGH there are numerous reports on the occurrence of pancytopenia associated with chronic exposure to benzene, only a few papers deal with the problem of the outcome and the development of leukemia among pancytopenic patients with chronic benzene poisoning.[1,2] Hunter reported ten fatal cases of a total of 89 pancytopenic patients with chronic exposure to this aromatic hydrocarbon.[3] In Germany 164 cases of benzene-induced aplastic anemia were encountered between 1913 and 1928; 27 of them were fatal! This corresponds to a mortality rate of 16.4%. Six of seven cases studied by Nilsby were fatal.[5] Contrary to this, in another report from Sweden only 2 cases of 60 were fatal.[6] On the other hand, Vigliani and Forni studied 83 patients with benzene-induced hematotoxicity in the provinces of Milano and Pavia;[7] all of the 50 patients who were still alive at that writing had aplastic anemia, and 19 patients with acute leukemia and 14 with aplastic anemia in this series ended fatally. The discrepancies concerning mortality in cases of pancytopenia associated with chronic exposure to benzene are obvious.

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Convincing data related to the outcome and the occurrence of leukemia in pancytopenic patients with chronic exposure to benzene were recently obtained in a long-term study among pancytopenic patients chronically exposed to this chemical in Istanbul. Prior to the period of 1955–1960, benzene was rarely used in Istanbul or in any other cities of Turkey. At that time, shoeworkers were preparing their adhesives by processing rubber in gasoline containing trace amounts of benzene.[8] As they discovered that adhesives prepared with benzene were cheaper as well as extremely practical, they replaced their customary adhesives with these new products. Starting in 1961 cases of aplastic anemia and from about 1967 cases of leukemia due to chronic benzene poisoning began to occur. The details of blood changes in 34 pancytopenic patients with long-term exposure to benzene were published subsequently;[9,10] the overall mortality rate among these patients was 26.4%. By 1977 the number of pancytopenic patients we had studied increased to 46.

In this paper we report the mortality rate and the occurrence of leukemia among 44 pancytopenic patients (two have been lost to followup) associated with chronic exposure to benzene.

MATERIALS AND METHODS

The series comprises 41 males and 3 females ages 15–57 yr (average 31). Of these 44, 38 were initially admitted to the hematology department of Internal Clinic of Istanbul Medical School; after discharge they were followed by us for periods of 2–17 yr. Six patients were studied by us only in the outpatient department. Thirty-nine of our patients were described elsewhere.[9-11] The followup periods on the pancytopenic patients who recovered completely were 2–17 yr: > 10 yr in 10, 5–10 yr in 11, and < 5 yr in 2 cases. Thirty-four patients were shoeworkers, two manufactured leather objects. two were car painters, one worked in a factory where benzene was used, one made benzene-containing glues, one was a radio technician, one was a whistlemaker, one was a handbag worker, and one was a furniture manufacturer. They had been subjected to high concentrations of benzene (150–650 ppm) for periods of 4 mo to 15 yr (mean 6.7 yr). The daily exposure to benzene varied from 15 min to 8 hr. Thirty of the patients were exposed to a high concentration of benzene for not less than 8 hr.

The benzene content of the adhesives available during 1970–1972 was determined by gas chromatography in the laboratory of the Turkish department of labor (IŞGÜM), Ankara[12] as 9%–88% (average 50%). The working conditions of most of the pancytopenic patients were hardly good; their working places were unhygienic and poorly ventilated.

In the period of pancytopenia, the basic therapy for these patients consisted of supportive care with appropriate antibiotics for infections, fresh blood in plastic bags, and whole blood transfusions for thrombocytopenia and anemia. Furthermore, 10 patients received only androgen, 10 corticosteroids and androgen together, 11 phytohemagglutinin, and 9 oral oxymetholone. The results of these treatments were partly described elsewhere.[10,13]

The hematologic methods were all standard. Blood counts in some patients were performed with a Coulter Counter model ZF. Platelet counts were determined with a phase-contrast microscope using the Brecher-Cronkite technique.[14] HbF was determined by the method of Singer et al.[15] HbA_2 was estimated quantitatively by DEAE-cellulose chromatography and starch gel electrophoresis.[16,17] With these methods normal values for HbA_2 are 2%–3.2% for the former and 1.5%–4% for the latter method. The concentration of benzene vapor in the air of the working environments of the patients was measured by a Drager Multigas detector (Model 21/23, Lubeck, Germany). The absorption spectra of benzene used for the preparation of adhesives was determined by using a Varian ultraviolet spectrophotometer Model 635 according to the technique described by Gillam and Stern.[18]

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Table 1. Relationship Among Age, Duration of Exposure, and Outcome, Including Development of Leukemia, in 44 Pancytopenic Patients Associated With Chronic Exposure to Benzene

	No. of Patients/ Percentage	Age (yr)	Duration of Exposure (mo)
Pancytopenia, complete remission	23/52.3%	26.87 ± 9.50	65.43 ± 42.30
pancytopenia, fatal outcome	14/31.8%	37.0 ± 9.81	93.0 ± 41.49
Pancytopenia, leukemia developed	6/13.6%	35.0 ± 7.46	94.67 ± 60.17
Pancytopenia. myeloid metaplasia developed	1/2.3%		
Pancytopenia. overall fatal outcome	21/47.7%	36.0 ± 8.98	93.62 ± 45.0

Mean ± SD.

RESULTS

The absorption spectra of benzene available in Turkey showed that despite the absence of benzo(a)pyrene,* the well-known carcinogenic agent, it contained some impurities such as toluene and naphtalen and also possibly xylene, phenathren, and chrysen.

Relationship among, age, duration of exposure, and outcome including development of leukemia. These are given in Table 1. Complete remission was obtained in **23** patients? **(52.3%).** Fatal outcome due to the complications of pancytopenia, such as infection or bleedings, occurred in **14** patients **(31.8%);** 7 pancytopenic patients died in the first year following diagnosis, 6 in the second, and only one died after 5 yr of survival. In **6** pancytopenic patients **(13.6%)** leukemia developed after a period of 6 mo to 6 yr. In most of these patients clinical and hematologic findings of pancytopenia improved considerably or even disappeared, but in spite of such improvement leukemia occurred. In 5 patients leukemia developed during the course of pancytopenia, in 1 patient 6 yr after complete recovery.

Five patients were not reexposed to benzene following diagnosis of aplastic anemia. One patient died from myeloid metaplasia **9** yr after recovery." The mean age of the pancytopenic patients who recovered completely was **26.87** yr, 37.0 for the pancytopenic patients with fatal outcome and **35.0** for those in whom leukemia developed. Furthermore, the mean age of **21** pancytopenic patients who died **(36.0** yr) was significantly higher ($p < 0.01$, $t = 3.2681$) than that of **23** pancytopenic patients with complete remission **(26.87** yr). On the

*We will not discuss the possibility of this carginogen in the development of leukemia in our pancytopenic patients because of the absence of benzo(a)pyrene in benzene available in Turkey. On the other hand, at present it is extremely difficult to interpret the possible role of other impurities in the development of leukemia in our pancytopenic patients.

†In 1 of these **23** patients with complete recovery, carcinoma of the rectum developed. The relationship between this malignancy and chronic exposure to benzene is open to discussion.

Table 2. Relationship Between Data Concerning Pancytopenia and Outcome, Including Development of leukemia, in 44 Patients With Chronic Exposure to Benzene (Mean ± SD)

	With CR (n = 23)	With Fatal Outcome (n = 14)	Leukemia Developed (n = 6)	With Overall Fatal Outcome (n = 21)
Hb (g/dl)	6.33 ± 2.04	5.19 ± 1.19	5.75 ± 1.09	5.33 ± 1.14
PCV	0.21 ± 0.07	0.17 ± 0.04	0.21 ± 0.03	0.18 ± 0.04
WBC x 10^9/liter	2.47 ± 0.85	2.06 ± 0.85	2.18 ± 1.08	2.11 ± 0.88
Neutrophils x 10^9/liter	1.51 ± 0.73	0.76 ± 0.26	1.28 ± 0.89	0.96 ± 0.58
Platelets x 10^9/liter	87 ± 56	56 ± 49	64 ± 44	61 ± 46

other hand, the duration of exposure was 65.43 mo in the pancytopenic patients who recovered completely and was 93.0 and 94.67 mo respectively, in those who died from complications of pancytopenia and in those in whom leukemia developed. Furthermore, the duration of exposure was significantly shorter ($p < 0.05$, $t = 2.2194$) in 23 pancytopenic patients who recovered completely (65.43 mo) than in 21 pancytopenic patients with overall fatal outcome (93.62 mo).

Although the concentration of benzene in all working places was not less than 150 ppm, 8 of 14 pancytopenic individuals with fatal outcome were subject to comparatively shorter daily exposure. Furthermore, all pancytopenic patients in whom leukemia developed were heavily exposed to benzene during long working hours. Although in one of these patients the duration of exposure was only 6 mo, his daily exposure was over 8 hr at a benzene concentration of 150 ppm.

Relationship between data concerning pancytopenia and the outcome, including development of leukemia. This is shown in Table 2.

Relationship between types of bone marrow cellularity and outcome, including development of leukemia. Of 42* pancytopenic patients, 21 had hypocellular bone marrow. This was observed in 17 of these patients 1–6 mo after appearance of the first signs or symptoms attributable to pancytopenia, and 6–12 mo in 3 patients; only in 1 was it as long as 2 yr. Of these 21 pancytopenic patients with hypocellular bone marrow, 11 died from complications of aplastic anemia, and in 5 patients leukemia developed later. Contrary to this, only 1 of 13 pancytopenic patients with normocellular bone marrow died. The normoplastic bone marrow was found in 10 of 13 pancytopenic patients 1–6 mo after appearance of the first clinical manifestations; in the remaining 3 this finding was observed in a symptomless period during a survey of workers using benzene-containing materials. On the other hand, 4 of 8 pancytopenic patients with hypercellular bone marrow recovered completely, and 2 died from complications of pancytopenia: in 1 of these 2 leukemia developed 1 yr later, and in the other the occurrence of myeloid metaplasia 9 yr after complete recovery was the cause of death. In 7 of these 8 pancytopenic patients a hyperplastic bone marrow was found 1–6 mo following the appearance of the first signs or symptoms attributable to pancytopenia; in 1 this period was 2 yr.

*In two pancytopenic patients bone marrow puncture was not performed.

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al e	Leukemia Developed	With Overall Fatal Outcome
)	(n = 6)	(n = 21)
.19	5.75 ± 1.09	5.33 ± 1.14
.04	0.21 ± 0.03	0.18 ± 0.04
.85	2.18± 1.08	2.11 ± 0.88
.26	1.28 ± 0.89	0.96 ± 0.58
9	64 ± 44	61 ± 46

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Table 3. Relationship Between Levels of HbF and Outcome, Including Development of leukemia, in 32 Pancytopenic Patients With Chronic Exposure to Benzene

Pancytopenia	No. of Patients	Fetal Hb (%) (Mean ± SD)
Complete remission	22	1.33 ± 4.79
Fatal outcome	5	5.28 ± 2.42
Leukemia developed	4	17.85 ± 20.81
Myeloid metaplasia developed	1	14.0
Overall fatal outcome	10	11.18 ± 13.67

Two pancytopenic patients with high fetal Hb level (brothers), one with fatal outcome and the other with complete remission, were not included in this table because both were also β-thalassemic heterozygotes. They were described elsewhere [9]

Relationship between levels of HbF and A, and outcome, including development of leukemia. This is shown in Table 3. Because different methods were used in determining HbA_2, the mean level of HbA_2 is not included in Table 3. In 22 pancytopenic patients who recovered completely, the mean level of HbF was 1.33%. This value was a little lower in 5 pancytopenic patients with fatal outcome (5.28%), but this difference is statistically insignificant. On the other hand, in 4 pancytopenic patients in whom leukemia developed the percentage rate was comparatively higher (17.85%), due mainly to a high percentage of HbF (48%) found in 1 patient. The level of HbA_2 was slightly or moderately decreased in 5 of 22 pancytopenic patients with complete remission (1.5%-1.95%). On the other hand, HbA_2 was slightly decreased only in 1 of 5 pancytopenic patients with fatal outcome. Furthermore, in 3 of 4 pancytopenic patients in whom leukemia developed HbA_2 was decreased. In one of these pancytopenic patients in whom later preleukemia developed the levels of HbF and A, were 48% and 0.67%, respectively. In another pancytopenic patient in whom acute erythroleukemia developed, HbF and A, levels were 15% and 1.8%, respectively In a third pancytopenic patient the levels of HbF and A, were 6.4% and 2.6%, respectively; when preleukemia developed 6 yr after recovery these mounts were 11.5% and 1.6%, respectively.

DISCUSSION

Pancytopenia similar to that of aplastic or hypoplastic anemia is the classical finding of human benzene hematotoxicity. As Goldstein rightly pointed out, the great variation in the cellularity of the bone marrow tissue, ranging from hypercellularity to acellularity, is the cause of hesitation of some investigators to call all such disease aplastic anemia.' In our series the overall mortality was 47.7%, slightly more favorable than mortality rates obtained in series of acquired aplastic anemia of various etiologies.[20–23] On the other hand, there was a wide variation in the range of mortality of the pancytopenic patients with chronic exposure to benzene according to the cellularity of the bone marrow. Of 21 pancytopenic patients with hypocellular bone marrow, 16 died either from the complications of aplastic anemia or from leukemia. In contrast, only 1 of 13 pancytopenic patients with normoplastic bone marrow showed fatal outcome.

There was a certain relationship among some clinical findings such as age,

duration of exposure, and outcome of pancytopenic patients with chronic exposure to benzene. The mean age of the pancytopenic patients with complete remission was significantly less than in those with overall fatal outcome, 26.87 and 36 yr, respectively. Similarly, the mean duration of exposure was significantly shorter in the pancytopenic patients who recovered completely than those with overall fatal outcome, 65.43 and 93.62 mo, respectively. Despite this, in one of the patients in whom preleukemia developed the duration of exposure was very short, only 4 mo, but this patient was heavily exposed to benzene during this short period.

Individual susceptibility and genetic predisposition are also very important factors in the occurrence of chronic benzene poisoning, including the development of leukemia.[24-26] Unlike the age and duration of exposure, with the exception of mean values of neutrophils the findings of peripheral blood could not be correlated with the outcome of benzene-induced pancytopenia.

There was no relationship between the levels of HbF and A_2 and the outcome of the pancytopenic patients. Increased levels of HbF with or without decreased levels of HbA_2 were found in pancytopenic patients both with complete remission and with fatal outcome, but very high levels of HbF and very low levels of HbA_2 are encountered only in leukemic states, unless the presence of a &thalassemic gene or a gene for hereditary persistence of fetal Hb is eliminated. In one of our patients, a very low level of HbA_2 and a high level of HbF had been found already during the preceding pancytopenic stage, whereas leukemia developed 9 mo later. As we pointed out previously,'." this observation suggests that very low levels of HbA_2 with or without high levels of HbF during the pancytopenic state may be a sign of leukemia.

In cytogenetic studies performed by Erdoğan and Aksoy, in 10 of 44 pancytopenic patients, 6 with complete remission, 2 with fatal outcome, and 2 in whom leukemia developed later, there was no relationship between cytogenetic findings and outcome, including the development of leukemia following benzene-induced pancytopenia.[27,28]

The development of leukemia in 6 of 44 pancytopenic patients with chronic exposure to benzene should be stressed here. Similarly, Harnberg et al.[29] observed a case of leukemia during a 9-yr followup of 147 individuals occupationally exposed to high levels of benzene; 107 showed certain degrees of hematologic abnormalities. Furthermore, Vigliani and Forni[7] in Italy found 19 cases of leukemia among 83 pancytopenic workers exposed chronically to benzene. In addition, during a followup period of 9 yr the present authors and their associates encountered one case of acute leukemia among 217 apparently healthy workers with chronic exposure to benzene;[8,30] 51 of them showed hematologic abnormalities.

The development of leukemia in 6 of 44 pancytopenic patients is further evidence for the leukemogenic effect of benzene in man. Moreover, studies on the incidence of leukemia among shoeworkers in Istanbul during 1967-1975 show a rate of 13/100,000, a statistically significant increase over-that within the general population.[8,26,31] Furthermore, the decline of the annual number of leukemic shoeworkers in Istanbul following the substitition for and prohibition of benzene after 1969 is further confirming evidence for the leukemogenic effect of benzene in man.[8,26]

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