

# Leukemia in Shoe-Workers Exposed Chronically to Benzene

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From 1967 to September 1973, 26 patients with acute leukemia or preleukemia were seen in Istanbul among 28,500 shoeworkers exposed chronically to benzene. The incidence of leukemia among these workers was 13/100,000, which is a marked

and statistically significant increase over that for leukemia in the general population and provides cogent evidence for the clinical impression of a leukemogenic effect of benzene in man.

**A**LTHOUGH THERE HAVE BEEN numerous reports<sup>1</sup> of leukemia associated with chronic benzene exposure since its original description by LeNoire et Claude,<sup>2</sup> some doubt still exists as to the causal relationship between benzene exposure and leukemia.<sup>3,4</sup> This uncertainty results chiefly from conflicting reports on the effect of benzene exposure in experimental animals and the lack of statistical data showing an increased incidence of leukemia among individuals known to have been exposed to benzene.

In Istanbul, and to a lesser extent throughout Turkey, there have been a number of cases of chronic benzene poisoning in workers involved in the manufacture of shoes and slippers. In this industry, benzene is used as a solvent. Of 34 patients with pancytopenia, six have been shown to have acute leukemia,<sup>7,9,10</sup> and one myeloid metaplasia which followed aplastic anemia.<sup>11</sup> The occurrence of acute leukemia in shoe workers exposed chronically to benzene was first noted in Istanbul in 1967; since then a number of cases have been observed. We have established an incidence of leukemia of 13 per 100,000 in shoe workers in Istanbul which is clearly greater than that of the general population. Here, we report these findings and discuss some clinical and hematologic observations in these patients.

## MATERIALS AND METHODS

Official records of Istanbul indicate that there are 28,500 workers involved in the shoe, slipper, and handbag industry in which benzene is used as a solvent. During the period from 1967 to 1973, 17 workers who had been exposed to benzene were admitted with acute leukemia or preleukemia\* to the Second Internal Clinic at Istanbul Medical School (five patients have been previously described<sup>7,10</sup>). In addition, nine other shoe workers with acute leukemia or preleukemia were seen in other hospitals in Istanbul—five at the First Internal Clinic at Istanbul Medical

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\*Another worker with acute lymphoblastic leukemia when exposed to benzene was not included because his occupation differed; he was a furniture worker. Since submission of this paper, two cases of acute erythroleukemia due to benzene exposure were seen but are not included.

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Table 1. Some Clinical and Hematologic Data Including Some Findings of Bone Marrow in Twelve Shoemakers With Acute Leukemia or Preleukemia

|                                                         | Case 1†† | Case 2  | Case 3  | Case 4  | Case 5  | Case 6 | Case 7 | Case 8 | Case 9  | Case 10 | Case 11†† | Case 12†† |
|---------------------------------------------------------|----------|---------|---------|---------|---------|--------|--------|--------|---------|---------|-----------|-----------|
| Age (years)                                             | 39       | 58      | 22      | 32      | 20      | 25     | 23     | 28     | 36      | 39      | 48        | 43        |
| Type of leukemia                                        | A. Myl.  | A. Myl. | A. Myl. | A. Myl. | A. Lym. | A. Er. | A. Er. | A. Er. | A. Pro. | Pr. L.  | Pr. L.    | Pr. L.    |
| Duration of exposure (years)                            | 7        | 14      | 6       | 12      | 1       | 15     | 11     | 15     | 2.5     | 10      | 10        | 15        |
| Duration of symptoms (months)                           | 7        | 5       | 3       | 4       | 2       | 6      | 5      | 2      | 2       | 6       | 15        | 12        |
| Red blood cells (millions/cu mm)                        | 3.19     | 3.60    | 1.78    | 2.25    | 1.52    | 2.32   | 1.82   | 1.43   | 3.06    | 1.61    | 3.00      | 1.46      |
| Hemoglobin (g/100 ml)                                   | 5.4      | 9.8     | 5.7     | 5.3     | 4.6     | 5.4    | 5.4    | 4.1    | 7.4     | 4.5     | 6.3       | 3.2       |
| White blood cells (per cu mm)                           | 18,600   | 13,000  | 3,000   | 2,400   | 7,800   | 5,400  | 3,800  | 4,400  | 1,800   | 400     | 6,400     | 2,600     |
| Reticulocytes (%)                                       | 5.4      | 2       | 0.6     | 1       | 1.5     | 1.4    | 15.2   | 0.8    | 2       | 0       | 1.4       | 0.8       |
| Platelets (per cu mm)                                   | 55,000   | 110,000 | 30,000  | 10,000  | 103,000 | 70,000 | 10,000 | 25,000 | 117,000 | 10,000  | 140,000   | 50,000    |
| Hematocrit (%)                                          | 22       | 35      | 15      | 19      | 14      | 19     | 18     | 13     | 27      | 19      | 23        | 11        |
| Nucleated red cells/100 WBC (in peripheral blood smear) | 15       | 0       | 0       | 0       | 0       | 27     | 16     | 19     | 1       | 2       | 10        | 0         |
| Fecal urobilinogen (Ehrlich Units /100 g of feces)      | X        | X       | X       | X       | 600     | 320    | 480    | 600    | X       | X       | X         | X         |
| Serum LDH (N:200-400 Wroblewsky Units)                  | 750      | X       | X       | X       | X       | 678    | 1224   | X      | X       | 840     | X         | 426       |
| Screening test for muremidase in urine                  | -        | X       | +       | X       | -       | -      | -      | -      | X       | X       | -         | X         |
| Bone marrow findings†                                   |          |         |         |         |         |        |        |        |         |         |           |           |
| Myeloblast (%)                                          | 15       | 89      | 75      | 80      | 0       | 9      | 2      | 0      | 1       | 0       | 0         | 3         |
| Promyelocyte (%)                                        | 3        | 0.5     | 0       | 1       | 0       | 5      | 1      | 0      | 40      | 0       | 2         | 2         |
| Lymphoblast (%)                                         | 0        | 0       | 0       | 0       | 28.5    | 0      | 0      | 0      | 0       | 0       | 0         | 0         |
| Proerythroblast (%)                                     | 1        | 0       | 0       | 0       | 1       | 1      | 7      | 59     | 0       | 0       | 20        | 3         |
| Megaloblast (%)                                         | 0        | 0       | 0       | 0       | 0.5     | 1      | 8      | 4      | 0       | 12      | 0         | 2         |
| Giant erythroid precursor (%)                           | 0        | 0       | 0       | 0       | 0       | 0      | 0      | 0      | 0       | 72      | 0         | 0         |
| Myeloid series (%)                                      | 45       | 94      | 94      | 87      | 31.5    | 26     | 43     | 3      | 86      | 6       | 16.5      | 52        |
| Erythroid series (%)                                    | 39       | 1.5     | 4       | 6       | 4.5     | 61     | 49     | 95     | 3.5     | 90      | 73        | 35        |

\*In these patients, the type of anemia was hypochromic microcytic throughout their illness.

†In their peripheral blood smears, myeloblasts ranging between 3% and 55% were found.

‡All bone marrows were hyperplastic.

A., Acute; Myl., Myeloblastic; Lym., Lymphoblastic; Er., Erythroblastic; Pro., promyelocytic; Pr.L., Preleukemia.

X: Not performed.

School,<sup>13</sup> three at the Therapeutics Clinic at Cerrahpasa Medical School,<sup>14</sup> and one at the Internal Clinic at that school.<sup>15</sup> The working conditions in the industry are not good; their shops usually are small, not hygienic, and poorly ventilated; the concentration of benzene was found to reach a maximum of 210-650 parts per million when adhesives containing benzene were in use (Measured by Dräger Gasspurgerat/Multi-Gas Detector Mod. 21/23, Lubeck, Germany).

## RESULTS

Clinical and hematologic data on 12 patients with acute leukemia or preleukemia are presented in Table 1. In Table 2, the types of leukemia and their frequency among the 26 patients diagnosed in Istanbul from 1967 to 1973 are compared with those previously reported by Goguel et al.<sup>16</sup> in 23 workers who developed acute leukemia or preleukemia after exposure to benzene. Acute myeloblastic leukemia which was seen in 14 of the 26 workers in our series was the most common diagnosis. The duration of exposure to benzene varied from 1 to 15 yr with a mean of 9.7 yr; the average age at the time of diagnosis was 34.2 with a range of 16-58 yr.

During the 7-yr period of the study, 26 patients with acute leukemia or preleukemia were observed among a group of 28,500 workers at risk. Thus, there was an incidence of 13 per 100,000. This incidence was significantly greater ( $p > 0.02$ ) than the overall incidence of leukemia in the general population which was 6/100,000.<sup>17</sup> The peak incidence of leukemia, 19.7 cases/100,000, occurred in the period between 1971 and 1973.

## CLINICAL FEATURES

One of the new patients (case 12) and five of the overall groups of 26 presented with pancytopenia. Fever of moderate or severe degree was present in all. With one exception (case 11), there were severe hemorrhagic manifestations, such as purpura, ecchymoses, epistaxis, hematuria, etc. Splenomegaly was present in three and lymphadenopathy in one.

The diagnosis of preleukemia was made in three patients (10,11,12). In one patient there was an initial period of pancytopenia after which splenomegaly developed. The initial bone marrow was aplastic, but subsequent bone marrows were hyperplastic with megaloblastoid erythropoiesis and erythroid hyperplasia; giant erythroid precursors varied from 38%-72%. Although serum folate

**Table 2. The Types of Acute Leukemia in 26 Shoe-Workers With Chronic Exposure to Benzene and in 23 Workers Exposed Chronically to Benzene Studied by Goguel et al.<sup>16</sup>**

| Types of Acute Leukemia      | Present Study   |            | Study of Goguel et al. |            |
|------------------------------|-----------------|------------|------------------------|------------|
|                              | Number of Cases | Percentage | Number of Cases        | Percentage |
| Acute myeloblastic leukemia  | 14              | 53.9       | 11                     | 47.8       |
| Preleukemia                  | 4               | 15.4       | 5                      | 21.7       |
| Acute erythroleukemia        | 3               | 11.5       | 2                      | 8.7        |
| Acute lymphoblastic leukemia | 3               | 11.5       | 2                      | 8.7        |
| Acute monocytic leukemia     | 1               | 3.8        | 1                      | 4.3        |
| Acute promyelocytic leukemia | 1               | 3.8        |                        |            |
| Unidentified                 |                 |            | 2                      | 8.7        |
| Total                        | 26              |            | 23                     |            |

levels were low, he failed to respond to treatment with folic acid. In view of this, we felt that the patient had either preleukemia or acute erythroid leukemia. A second patient (case 11) had hypochromic microcytic anemia with a normal serum iron. The morphologic findings, indices, and hemoglobin analysis were consistent with heterozygous  $\alpha$  or  $\beta$  thalassemia with normal levels of  $A_2$  and F hemoglobins. Genetic studies confirmed this assumption. The patient also had a persistent pseudo-Pelger-Huet anomaly and erythroid elements in the peripheral blood. Myeloblasts were present in the peripheral blood during the final stages of his illness; at that time, erythroid elements comprised 74% of the nucleated cells in the bone marrow, and there were 20% proerythroblasts. There were no frank signs of increased hemolysis. We considered this patient as having preleukemia or acute erythroleukemia. The third patient (case 12) had pancytopenia prior to the onset of preleukemia. At that time, his bone marrow was hyperplastic. A year later when the patient had recovered from pancytopenia he was again exposed to benzene, and a severe anemia, leukopenia, and recurrent pulmonary infections ensued. The bone marrow continued to be hyperplastic and was consistent with but not diagnostic of leukemia. However, prior to his death, he developed a peripheral blood picture more consistent with leukemia, there being 15% myeloblasts.

In three patients,<sup>6-8</sup> the diagnosis of acute erythroleukemia was made. These patients had 16-29 nucleated red cells/100 white cells in the peripheral blood and 49%-95% erythroid elements in a hyperplastic bone marrow. In one of these patients, proerythroblasts comprised 59% of bone marrow nucleated cells. Megaloblastic changes were also observed in these patients. One of these patients (case 8) was thought to have a significant amount of ineffective erythropoiesis as well as early red cell destruction; he had striking reticulocytosis, increased osmotic fragility, and increased fecal urobilinogen, as well as a decrease in serum haptoglobin.

#### DISCUSSION

A number of physical and chemical agents have been thought to be implicated as etiologic factors in leukemia. Among these, however, ionizing radiation is the only one which has been shown conclusively to have a leukemogenic effect. These conclusions are based on the high incidence of leukemia among Japanese exposed at Hiroshima<sup>18,19</sup> and the British patients treated with x-rays for ankylosing spondylitis.<sup>20</sup> There is a strong inferential evidence, however, to suggest that benzene may have a role in the induction of leukemia. The incidence of leukemia among workers chronically exposed to benzene, described herein, provide further proof for an etiologic role for benzene in leukemia. The incidence of leukemia of 13/100,000 in the exposed shoe workers was significantly greater than that seen in the general population.

It is of interest that, in the patients in this study, all had acute leukemia. In this respect, our experience is similar to that reported by Vigliani and Saita.<sup>21,22</sup> We observed, as have others, that the morphologic type of leukemia among those exposed to benzene is variable, but acute myeloblastic leukemia is the most common. The frequency of various morphologic types in our patients was also similar to that reported by Goguel<sup>16</sup> in patients exposed to benzene.

In the present study, the incidence of leukemia during the first 4 yr was somewhat lower than it was in the last 3. Only nine cases were diagnosed between 1967 and 1971, whereas 17 cases were seen in the last 3 yr. The latter would have given an incidence of 19.7/100,000. For this reason, we searched for additional possible leukemogenic factors but were unable to detect any other than benzene.

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