British Journal of Haematology, 1987, 66, 209–211

# Chronic lymphoid leukaemia and hairy cell leukaemia due to chronic exposure to benzene: report of three cases

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*Received* 10 *March 1986: accepted* for *publication 9 December 1986*

Summary. Three cases of chronic leukaemia. hvo with chronic lymphoid and one with hairy cell leukaemia are reported. These three leukaemic patients belonged to a series of 58 leukaemic patients with chronic exposure to benzene. The low percentage of chronic leukaemias in this series is discussed.

Since 1897 numerous cases of leukaemia associated with chronic exposure to benzene have appeared in the medical literature. Despite this, the exact relationship between this chemical and leukaemia was well established only recently by the studies performed among shoe-workers in Istanbul (Aksoy. 1980: Aksoy *et nl.* 1976. 1987). Between 1967 and 1975 **40** leukaemic patients with chronic exposure to benzene were admitted to the haematology departments in Istanbul, 34 of them being detected **among** a group of 28500 shoe-workers. The concentration of benzene in the working environment of these workers ranged between 150 **and** 210 and rarely 650 ppm. The benzene content of the adhesives available during the period of 1970 and 1972 was between 9% and 88% **(Aksoy** & Erdem. 1978). The crude incidence of leukaemia among this group was 13·59 per 100000 which is significantly higher ($P<0·01$) than 6 per 100000 for leukaemia in the general population (Aksoy *et al.* 1976, 1987). The peak incidence of leukaemia among shoe-workers with chronic exposure to benzene in Istanbul was in 1973. being 21·7 per 100000. Following the 'phase-out' of benzene in Istanbul the annual number of leukaemic workers decreased rapidly (Aksoy. 1980). The decline of leukaemia after 'phase-out' of benzene supports the assumption of a leukaemogenic effect of benzene on the shoe-workers studied.

In addition, in a recent study. the present author and his associates have observed two cases of acute leukaemia. one myeloblastic and the other lymphoblastic. in a 6-year period in a modern tyre cord plant around Izmit. a city close to Istanbul (Aksoy. 1985: Aksoy *et al.* 1987). In this plant approximately 550 workers were employed. The concentration of benzene measured by gas chromatography in one place of the plant was 110 ppm. One of the solvents used in the auxillary repair shop had a benzene content of nearly 5%. The incidence of leukaemia **among** the workers **was** 60.6 per 100000.

Although acute leukaemia in chronic benzene toxicity predominates in several studies such as Vigliani & Forni **(1976).** Aksoy *et al* (1974) **and** Infante *et al* (1977), there are several reports describing **the** frequent Occurrence of chronic myeloid leukaemia and even chronic lymphoid leukaemia following chronic exposure to benzene (Tareef *et al.* 1963: Goguel *et al.* 1965: Browning, 1963). Furthermore. in epidemiological studies among rubber workers performed by Monson & Nakano (1976). McMichael *et al* (1975) and Andelkoviç *et al* (1976). it was shown that the prominent type of leukaemia in chronic benzene toxicity was chronic lymphatic leukaemia. **On** the other hand. from 1967 to 1985 we have collected 53 cases of leukaemia due to chronic exposure to benzene (Aksoy *et al.* 1987). Despite the absence of chronic lymphoid leukaemia in **this** series. the present author suggested that this **type** of leukaemia might develop in chronic benzene toxicity (Aksoy *et al.* 1987). Indeed in 1985 we have observed five new cases of leukaemia possibly due to chronic exposure to benzene. **two** with acute myeloblastic, one with hairy cell **and** two **with** chronic lymphoid leukaemia.

The purpose of this paper is **to** report the above-mentioned three cases of chronic leukaemia associated with chronic exposure to benzene.

## MATERIALS AND METHODS

Three cases of leukaemia. two with chronic lymphocytic and one with hairy cell leukaemia are studied. These leukaemic patients belonged to a series of 58 leukaemic patients with chronic exposure to benzene observed in the

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period of 1967–85. From these 58 leukaemic patients with chronic exposure to benzene. three were chronic myeloid. two chronic lymphoid and one hairy cell leukaemia.

All haematological methods were standard. benzene content in the solvents and thinners were determined by a Varian gas chromatography in the Department of Chemical Engineering Faculty. Istanbul University. by Professor Dr Suheyla Özeriş. The concentration of benzene in the working environment in Istanbul during the period 1965–75 was det-rmined by a Drager multigas detector (Aksoy *et al.* 1974. 1987) and the concentration of benzene in the working environment was found to reach 210 ppm and rarely 650 ppm.

## CASE REPORTS

Case 1. a 43-year-old male, was examined by a physician because of cardiac complaints. The results of EKG were normal. He had never used chloramphenicol and had never been exposed to radiation. He has been the owner **of** a small printing shop in Istanbul **for** 2 years. For this purpose he mises pigmented dyes with solutions of toluene or methyl alcohol ketone. He is busy for 2 or 3 h daily in his plant. He usually sniffs the above-mentioned solutions for control purposes. Before this job he was in a shop selling other chemicals. Examination revealed a well-nourished and well-developed man. There was no hepatosplenogemaly and no lymphodenopathy. Laboratory data: haemoglobin 14·3 g/dl. RBC $4.8 \times 10^{12}$/l. PCV 0·45. platelets $380 \times 10^{9}$/l. WBC $29 \times 10^{9}$/l with 3% band forms. 25% polymorphonuclear neutrophils. 2% monocytes. 2% eosinophils and 68% lymphocytes. There were numerous Gumprecht's shadows in the blood smear. The bone marrow aspirate from sternum was hypocellular with 2% promyelocytes. 5% myelocytes. 7% metamyelocytes, 5% band **forms.** 8% segmented neutrophils. 3% polychromatic normoblasts. 5% orthochromatic **normo**blasts. 65% lymphocytes. Serum electrophoresis showed albumin 59·4%. alpha-I globulin 2·2%. alpha-2 'globulin 9·9%. beta-globulin 12·7% and gamma-globulin 15·8%. The toluene solution **used** contained 2·8% **of** benzene and 95.3% of toluene. The other solution of methyl metone contained no benzene.

Case 2. a 51-gear-old male. had some pains in the right quadrant. A haematological study disclosed a moderate leucocytosis with lymphocytic predominance. He **was** the owner of a plant where car components are produced or repaired. Because his office room was inside the active part of the plant. he was intermittently esposed to the solutions used during the workday. In his plant some cleaning solutions were also used: they contained no benzene determined by gas chromatography. On'the other hand. in the period 1955–65 the patient was the owner **of** a small plastic plant and he was intermittently exposed to some thinner containing **on** average 27·3% of benzene (Topuzoğlu. 1972). Laboratory data were: haemoglobin 12·8 g/dl. RBC $4.i \times 10^{12}$/l. PCV 0·43. platelets $410 \times 10^{9}$/l. WBC $23 \times 10^{9}$/l with 1% band forms. 24% polymorphonuclear neutrophils. 1% eosinophils. 1% monocytes and 73% lymphocytes. There rvere numerous Gumprecht's shadows. The bone marrow aspirate from the sternum was hypercellular **with** 4% myelocytes. 1% eosinophilic myelocytes. 3% metamyelocytes. 6% band forms. 7% segmented neutrophils. 2% polychromatic normoblasts. 5% orthochromatic normoblasts and 72% lymphocytes. Serum electrophrosis disclosed albumin 59.2%. alpha-1 globulin 3%. alpha-? globulin 11·2%. beta-globulin 11·1% and gamma-globulin 15·5%.

Case **3,** a 50-year-old manager in a plastic plant. was diabetic for 15 years. He had recurrent gluteal and inguinal furonculosis during the last 3 years. Because of these complaints. he was admitted to a hospital in Istanbul. Splenomegaly and pancytopenia were found. **A** spontaneous splenic rupture occurred during hospital stay and he was splenectomized successfully. After a short period he was admitted to the Department **of** Haematology. Kantonspital. Basel. There. Professor Dr Speck's diagnosis was hairy cell leukaemia: 16% of lymphoid cells contained tartrate resistant acid phosphatase. An interferon-therapy was recommended in this hospital. The patient was exposed heavily to benzene during the period 1957–65.

According to the patient his abuse of the thinners containing benzene was considerable. Sometimes for removing the dirt he cleaned himself with thinners containing benzene. Later he used polystyrene and polyethylene in his plant. On examination there was no lymphadenopathy. The liver was enlarged two fingerbreadths below costal margin. Laboratory data: haemoglobin 6.9 g/dl. RBC $2.3 \times 10^{12}$/l. PCV 0·22. platelets $40 \times 10^{9}$/l. WBC $2.3 \times 10^{9}$/l with 11% polymorphonuclear neutrophils, 1% band forms. 1% eosinophils, 1% monocytes and **86%** lymphocytes. **A** bone marrow puncture at sternum showed a hypocellular marrow with **2%** promyelocytes, 2% myelocytes, **3%** metamyelocytes, 3% band forms. **6%** polymorphonuclear neutrophils. **2%** polychromatic normoblasts. 5% orthochromatic normoblasts and **77%** small or large -lymphocytes. The patient is under treatment with alpha-2 interferon. He is in remission. His pancytopenia has resolved. At present he does not need any blood transfusion.

## DISCUSSION

**As** emphasized above, these three cases of leukaemia. two with chronic lymphatic and one with hairy cell leukaemia belongs to a series **of** leukaemia patients possibly due to chronic exposure to benzene (Aksoy **et** *al.* 1974. 1987: Aksoy. 1980. 1982). In this series acute leukaemia is predominant (89.7%) whereas chronic leukaemias are infrequent (10·3%). On the other hand. if we compare certain epidemiological data of our three cases of chronic leukaemia. two with chronic lymphoid and one with hairy cell leukaemia and those of 53 patients with acute leukaemia in our series. we find some differences. These are:

(1) The difference in the content of benzene used: during the period of 1970–72 it was between 9% and 88%. Despite this. benzene content of the solution used by case 1 with chronic lymphoid leukaemia was as low as 2·8%.

(2) The adhesives which were used nearly by all the workers with acute leukaemia in our series contained only benzene but not the other homologues of this chemical such as toluene and xylene. This fact is particularly evident during the period 1955–75 (Aksoy *et al.* 1976. 1987: Aksoy. 1985).

Contrary to this the solvent used in the workplace of the first patient with chronic lymphoid leukaemia (case 1) contained 95·3% of toluene and the second patient with chronic lymphoid leukaemia (case 2) was later exposed to different chemicals. Similarly the patient with hairy cell leukaemia (case 3), in addition to chronic exposure to benzene, later worked in a place where polystyrene and polyethylene were used. It has been shown in rats that there is a dose dependent metabolic interaction between benzene and toluene (Sato & Nakajima, 1979). When benzene or toluene was administered to rats in combination with the other, their disappearance rate from blood and the rate of urinary excretion of their metabolites were delayed compared with those when they were given separately. The metabolic interaction was found to be dose dependent. On the other hand, Checkorvay *et al* (1984) attempted to identify causative factors in 11 workers whose underlying cause of death was chronic lymphotic Leukaemia and they were identified from the same cohort reported by McMichael *et al* (1975). The case control analysis of chronic lymphoid leukaemia studied was extended to consider the risks associated with 24 types of solvents used in the cohort. Chekoway et *al* (1984) concluded that the association with chronic lymphoid leukaemia risk observed for the different solvents. most notably those with carbon tetrachlorid and carbon disulphide. were stronger than those detected for benzene.

(3) The great majority of the individuals with acute leukaemia in our series was exposed to a high concentration of benzene. between 150 and 210 ppm during all working hours. Contrary to this. five out of six patients with chronic leukaemia. huo with chronic myeloid. *two* with chronic lymphoid and one with hairy cell leukaemia, were exposed to benzene intermittently and for a short time during the daily work.

(4) The role of the age: as it is known the occurrence of chronic lymphoid leukaemia is unusual in persons younger than 30 years and becomes increasingly frequent with increasing age (Wintrobe *et al*, 1981). The ages of our patients with chronic lymphoid leukaemia were 43 and 50 respectively. The ages of these two patients may be considered relatively young for the occurrence of chronic lymphoid leukaemia. Despite this. the role of age in the development of the types of leukaemia in our patients is unclear. One of these two patients (case 2) was exposed to benzene at young age and the second (case 1) at middle age.

Considering these data. we suggest that striking difference concering the distribution of the types of leukaemia in chronic benzene toxicity in the groups from different studies may be partly explained by the exposure levels. the mode of exposure and the presence or absence of other homologues of benzene such as toluene and xylene or other chemicals. This problem needs further investigation.

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