



Acute Leukaemia in Two Generations Following Chronic Exposure to Benzene¹

M. AKSOY, S. ERDEM, GÜLTEN ERDOĞAN and GÜNÇAG DİNÇOL

Sections of Haematology and Genetics, Internal Clinic of Istanbul Medical School, Çapa, Istanbul

Abstract. Two cases of acute leukaemia, one lymphoblastic and the other myeloblastic, following chronic exposure to benzene in two relatives, a man and his paternal uncle, are presented. The possibly significant role of genetic predisposition is discussed. It was concluded that some genetic factors were triggered by chronic exposure to benzene in these patients.

Key Words
Acute leukaemia
Aetiological factors
Familial occurrence

The individual susceptibility has been considered one of the main factors in the incidence of chronic benzene poisoning [BROWNING, 1965]. There are several studies in favour of a great variation in individual susceptibility [REISEK and REJSKOVA, 1955; SAVILAHTI, 1955; AKSOY *et al.*, 1971]. The cause of this variation is not completely understood. According to BROWNING [1965] 'the most probable explanation lies in innate differences in the potency of different individuals to carry out the metabolic detoxication'. As early as 1922 REIFSCHNEIDER suggested a possible family susceptibility. We can give some examples from our series of chronic benzene poisoning in support of this assumption. **TWO** of our thalassaemic patients with aplastic anaemia due to chronic benzene exposure, one fatal, were brothers [AKSOY and ERDEM, 1969]. Also two patients with pancytopenia associated with chronic exposure to benzene, one fatal, were cousins [AKSOY *et al.*, 1972a].

The association between benzene exposure and leukaemia is known [VIGLIANI and SAITA, 1964; AKSOY *et al.*, 1972b]. Recently we studied two patients with acute leukaemia in two generations following chronic exposure to benzene; one was recorded shortly elsewhere [AKSOY *et al.*, 1972b].

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Case Reports

Propositus

M.T., a 24-year-old University student, was admitted to the 2nd Internal Clinic of Istanbul Medical School because of generalized lymphadenopathies. Six years earlier he had started to work as a shoemaker in a small shop where he used a glue containing a high percentage of benzene. After 4 years he left this job.

Physical examination. There were non-tender lymphadenopathies of moderate size in the mandibular, cervical, axillar and inguinal regions. The spleen extended four and the liver two finger breadths below the costal margin. There were a few purpuric spots on his feet. Temperature between 36.4 and 37.5°C.

Laboratory data. Red blood cell count 3.8 million/mm³; haemoglobin 12.8 g/100 ml; haematocrit 33%; reticulocytes 3.2%; platelet count 15,000/mm³; white blood cell count 42,000/mm³ with 69% lymphoblasts, 11% segmented neutrophils, 1% band form and 19% lymphocytes. There were numerous basket cells in the peripheral blood smear. Bone marrow aspirated from the sternum was hypercellular with 96% lymphoblasts, 2% segmented neutrophils and 2% orthochromatic normoblasts. There were numerous cytoplasmic vacuoles in lymphoblasts. The urine was negative for lysozyme (muramidase). Haemoglobin F was 1%.

Course. Acute lymphoblastic leukaemia following chronic exposure to benzene was diagnosed. The patient was given a treatment consisting of combined 6-mercaptopurine 150 mg daily, prednisolone 50 mg daily and Vincristine 1 mg twice weekly. Six weeks later, the generalized lymphadenopathies and the hepatosplenomegaly disappeared. The patient's red blood cell count was 3.7 million/mm³; haemoglobin 10.1 g/100 ml; haematocrit 35%; platelet count 165,000/mm³; white blood cell count 7,600/mm³ with normal differential count. The patient is still in remission 6 months later.

Paternal Uncle of Propositus

A 43-year-old shoemaker with 6 years of benzene exposure had an acute myeloblastic leukaemia, 2 years after the recovery from aplastic anaemia. He was described as case 2 in a series of four patients with acute leukaemia following chronic exposure to benzene [AKSOY *et al.*, 1972b]. Following combined cytostatic therapy, the patient stayed in remission for 1 year, but hepatocellular damage due to methotrexate developed and he died from oesophageal bleeding.

Results of Cytogenetic Studies after Institution of Treatment (Performed by the method of MOORHEAD *et al.* [1960])

The propositus has no numerical abnormalities. Contrary to this, his uncle showed an extra chromosome in the C group. Two cell lines were observed: one with 46,XY (87%) and one with 47,XY C+ (13%). Similar structural abnormalities were found in the two patients. These were: achromatic lesions, dicentric chromosomes and secondary constrictions.

Comments

The *propositus* and his paternal uncle described previously elsewhere [Aksoy *et al.*, 1972b] represent acute leukaemia following chronic exposure to benzene. When we compare the case reports of the two relatives - uncle and nephew - with acute leukaemia, we notice certain differences. These are: (1) the *propositus* represents an example of acute lymphoblastic leukaemia and his paternal uncle had acute myeloblastic leukaemia, (2) although in the uncle acute myeloblastic leukaemia developed 2 years after the occurrence of aplastic anaemia, in the *propositus*, acute lymphoblastic leukaemia appeared without a preceding period of a pancytopenic state.

Here the question arises as to whether there is a coincidental occurrence of acute leukaemia in two generations and whether it is possible that both patients, uncle and nephew, have a common genetic predisposition to leukaemia which was triggered by chronic exposure to benzene as an extraneous factor. Before answering this question we shall have a very short look on our present knowledge on the aetiology of leukaemia.

Although the aetiology of leukaemia is obscure, there is considerable evidence showing the significant role of certain factors in the development of leukaemia. These are genetic predisposition, chromosomal abnormalities, ionizing radiation, exposure to benzene, possible viruses, etc. Several families are known in which two or more cases of leukaemia of acute and particularly of chronic lymphocytic type occurred either in the same or successive generations [BARBER and SPIERS, 1964; GUNZ, 1970; UNDRIZ and SCHNYDER, 1971; GOSH, 1972]. Another supporting evidence for genetic predisposition to acute leukaemia is the concordance of this haematologic disorder in identical twins [MACMAHON and LEVY, 1964]. The significant role of genetic factors is also observed when leukaemia is associated with congenital chromosomal defects. As an example, a leukaemia incidence of fifteen times the normal may be found among children with Down's syndrome (trisomy 21) [WALD *et al.*, 1961]. Furthermore, a high incidence of leukaemia has been encountered in several hereditary disorders associated with excessive chromosome breakage, such as constitutional aplastic anaemia or Fanconi syndrome [BLOOM *et al.*, 1966], Bloom syndrome [SAWITSKY *et al.*, 1966] and ataxia telangiectasia [HECHT *et al.*, 1966]. Apart from ionizing radiation, the significant role of benzene as an external factor in the aetiology of leukaemia is widely accepted. There are numerous examples confirming the aetiological relationship between chronic exposure to benzene and leukaemia [VIGLIANI and SAITA, 1964; COGUEL *et al.*, 1967; AKSOY *et al.*,

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972b]. On the other hand, chronic exposure to benzene can lead to chromosomal defects [TOUGH and COURT BROWN, 1965]. Some investigators considered this as a cause of leukaemia [VIGLIANI and SAITA, 1964]. Although there were some chromosomal abnormalities in both our patients with acute leukaemia, it is difficult to incriminate them as a cause of this haematologic disorder.

Considering the facts mentioned above one may suggest that in our two patients with acute leukaemia in two generations some genetic factors were triggered by chronic exposure to benzene.

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Request reprints from: Prof. M. AKSOY, Internal Clinic of Istanbul Medical School, Çapa, Istanbul (Turkey)