Haematological effects of chronic benzene poisoning in 217 workers

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Aksoy, M., Dinçol, K., Akgün, T., Erdem, Ş., and Dinçol, G. (1971). *Brit. J. industr. Med.*, 28, 296-302. Haematological effects of chronic benzene poisoning in 217 workers. A haematological study consisting of the determination of RBC, WBC, PCV, platelets, and differential counts was carried out, together with bone marrow puncture and haemoglobin analyses in appropriate cases, on a control population of 100 normal people and on 217 male labourers, 95% of whom worked with solvents containing benzene in small shops manufacturing shoes under unhygienic conditions. The concentration of benzene in the work-places ranged between 30 and 210 p.p.m., and the period of exposure between 3 months and 17 years.

In 51 of the 217 workers (23.50%) haematological abnormalities attributable to chronic benzene poisoning were detected. Thus, leucopenia was present in 9.70%, thrombocytopenia in 1.84%, leucopenia associated with thrombocytopenia in 4.6%, pancytopenia in 2.76%, acquired pseudo-Pelger-Huet anomaly in 0.46%, lymphocytosis in 0.46%, giant platelets in 0.46%, eosinophilia in 2.30%, basophilia in 0.46%, and eosinophilia associated with basophilia in 0.46% (the maximum normal levels for eosinophils and basophils were 8% and 2% respectively).

Acquired pseudo-Pelger-Huet anomaly was detected in a worker with heterozygous beta-thalassaemia (HbA₂ 4.1% and HbF 8.7%) in whom the only effect of benzene was on the leucocyte nuclei, all other haematological values being within normal limits. On the other hand, in 33.1% of the workers the haemoglobin was less than 12 g/100 ml and in 32.7% the PCV was less than 40% with the MCV ranging between 86 and 96 μm^3 . In none of them did MCV exceed 100 μm^3 . Thirty-one per cent. of these anaemic workers were treated with adequate doses of oral iron, which resulted, in all cases, in a complete disappearance of the anaemia. Therefore, it is difficult to attribute this anaemia to the effect of benzene alone.

Thus it is concluded that benzene exerts its harmful effect, primarily on the leucocytes, with eosinophilia and basophilia as inconstant findings, secondarily on the platelets causing thrombocytopenia, and finally on all three series giving rise to pancytopenia.

The deleterious effect of benzene on the haemopoietic system is well known. The harmful effect of this aromatic hydrocarbon is due to its widespread use as an excellent solvent. During the last few years numerous patients with aplastic anaemia and some with acute myeloblastic leukaemia due to chronic

benzene poisoning have been detected among shoemakers in Istanbul (Aksoy, Dinçol, Akgün, Erdem, and Dinçol, 1970a). Hence an investigation was carried out on 217 apparently healthy workers manufacturing shoes under unhygienic conditions with solvents containing benzene.

Material

Two hundred and seventeen apparently healthy male workers aged from 12 to 58 (mean 24.7) years were investigated, together with 100 male controls aged from 17 to 58 (mean 26.6) years who were randomly selected from among healthy and mostly young hospital personnel, medical students, and people accompanying patients to our outpatient department, whose living standards roughly resembled those of the workers who were investigated.

The working conditions of all workers were not good as their small shops were usually unhygienic and poorly ventilated. The concentration of benzene in the working environment, which ranged between 15 and 30 p.p.m. outside working hours, was found to reach a maximum of 210 p.p.m. when adhesives containing benzene were being used. The period of exposure to benzene ranged between 3 months and 17 years.

Methods

All haematological methods were standard. Haemoglobin determinations were carried out by the oxyhaemoglobin method using a standardized Klett-Summerson photoelectric colorimeter. PCV was determined in microhaematocrit tubes and platelet levels were assessed by an indirect counting method as modified by Aksoy, Dinçol, Dinçol, and Erdem (1970b), the results being checked in most instances by Brecher and Cronkite's direct method (1950). The morphology of platelets in the peripheral blood was also carefully studied in each case. In some cases spontaneous aggregation and adhesion as well as viscous metamorphosis were studied (Caen, Castaldi, Leclerc, Inceman, Larrieu, Probst, and Bernard, 1966; Balkuv and Ulutin, 1967). Smears of peripheral blood and bone marrow were stained by the May-Grünwald-Giemsa technique. Fetal haemoglobin determinations were performed by the method of Singer, Chernoff, and Singer (1951).

The concentrations of the benzene vapour in the working environment were measured by a Dräger Multigas Detector.¹

Results and comments

The results of the investigations carried out in 217 apparently healthy workers using materials containing benzene are shown (Table 1). They illustrate the known deleterious effect of benzene on the haemopoietic system. After a period ranging between 3 months and 17 years of rather heavy exposure to benzene serious effects of chronic benzene poisoning such as leucopenia, thrombocytopenia, leucopenia associated with thrombocytopenia, and pancytopenia were observed in 18.90% of the workers studied. Apart from that, this incidence increased to 23.50% if other findings possibly attributable to chronic benzene poisoning are added, such as acquired pseudo-Pelger-Huet anomaly, lympho-

¹Dräger Gasspürgerat/Multi-Gas Detector Mod. 21/23 Lübeck, Germany.

TABLE 1
RESULTS OBTAINED FROM HAEMATOLOGICAL
INVESTIGATION OF 217 APPARENTLY HEALTHY
WORKERS USING MATERIALS CONTAINING BENZENE

Type of haematological change	No. of workers with haematological changes	Haematological change (%)
Leucopenia ¹	21	9.70
Thrombocytopenia ² ..	4	1.84
Leucopenia associated with thrombocytopenia	10	4.60
Pancytopenia	6	2.76
Leucocytosis	5 ⁵	2.30
Leucocytosis associated with thrombocytosis ..	2 ⁵	0.92
Acquired pseudo-Pelger-Huet anomaly ..	1	0.46
Lymphocytosis	1	0.46
Giant platelets	1	0.46
Eosinophilia ³	5	2.30
Eosinophilia associated with basophilia ..	1	0.46
Basophilia ⁴	1	0.46

¹Leucopenia: WBC less than 4,000/mm³.

²Thrombocytopenia: platelets less than 144,000/mm³ by the method of Brecher and Cronkite (1950).

³Eosinophilia: eosinophils more than 8%.

⁴Basophilia: basophils more than 2%.

⁵See text.

cytosis, giant platelets, eosinophilia, and basophilia. On the other hand, the incidence of leucocytosis and leucocytosis associated with thrombocytosis observed in five and two workers respectively (Table 1) have not been added to the total incidence of haematological changes, as the authors are not sure that these findings are directly related to the well-established effects of chronic exposure to benzene.

The ages of the workers with haematological changes ranged between 12 and 58 years. Twenty-three of the 51 workers, i.e., 45% of the subgroup with haematological changes, were between 13 and 20 years of age. On the other hand, 45% of the total number of workers investigated were also aged between 12 and 20 years. Thus, as the two percentages do not differ from one another, it was concluded that there probably was no correlation between the ages of the workers and the haematological changes observed.

Table 2 shows the relation of the period of exposure to the incidence of haematological changes in 51 of 217 workers. From this Table the incidence appears to be independent of the time of exposure (the small differences in the individual incidences are not statistically significant, *P* approximately 0.5).

TABLE 2
RELATION OF PERIOD OF EXPOSURE TO INCIDENCE
OF HAEMATOLOGICAL CHANGES IN 51 OF
217 WORKERS

Duration of exposure (yr)	All exposed workers		Workers with haematological changes		Incidence $\frac{B}{A} \times 100$
	No. (A)	%	No. (B)	%	
Less than 1	16	7.37	5	9.81	31
1–	109	50.23	24	47.05	22
5–	73	33.64	18	35.29	25
10–17	19	8.76	4	7.85	21
	217	100.00	51	100.00	

This could be interpreted as meaning that all haematological changes occur (or start) in the first year of exposure. Alternatively, if the proportion of workers from the affected group leaving the industry was higher than the proportion leaving from the total group, this could mask the appearance of cases occurring in later years of exposure.

Haematological changes observed in 217 workers exposed to benzene compared to 100 control subjects

Leucocytes As can be seen from Table 1, benzene exerts its effects mainly on leucocytes. According to our findings, the most frequently encountered haematological change in chronic benzene poisoning was in the white blood cell count which ranged between 2 100 and 12 800/mm³. Leucopenia alone was encountered in 21 workers (9.70%), leucopenia associated with thrombocytopenia in 10 (4.6%), and leucopenia as a part of pancytopenia in six (2.76%). In other words, in 37 workers (17.05%), the white cell count was less than 4 000/mm³.

The mean white blood cell count for 212 workers, five of whom were excluded because of the presence of acute rheumatic fever or a transient leucocytosis or both, was 5 468/mm³ (S.D. ± 1 827). The mean white cell count for the control group was 6 196/mm³ (S.D. ± 1 302) $P < 0.001$.

Besides these quantitative changes in the number of leucocytes, the effect of benzene on the leucocytes can be exemplified by the occurrence of acquired pseudo-Pelger-Huet anomaly, lymphocytosis, eosinophilia, basophilia, and eosinophilia associated with basophilia. These changes were observed separately in nine workers. Thus the harmful effects of benzene on leucocytes were detected in a total of 46 workers (21.19%).

Acquired pseudo-Pelger-Huet anomaly This was observed in a 19-year-old beta-thalassaemic worker

with seven years' exposure. His leucocyte count was 5 800/mm³, the majority of which had only bilobed nuclei. Band forms comprised 22% of the total leucocytes. Apart from that no other haematological abnormality was detected in the peripheral blood of this patient. On the other hand, a frank maturation arrest was found on examination of the bone marrow. Fifteen days after the cessation of exposure there was a marked decrease in the percentage of band forms. Haemoglobin analysis of this patient revealed increased levels of haemoglobins F and A₂, 8.9 and 4.1%, respectively. These findings are consistent with the diagnosis of heterozygous beta-thalassaemia. In this beta-thalassaemic heterozygote, the pseudo-Pelger-Huet anomaly had no familial character, and one month after the cessation of exposure the proportion of granulocytes showing this anomaly decreased rapidly.

In 1960 Paterni and Russo in Italy reported a severe and fatal case of chronic benzene poisoning in which an acquired pseudo-Pelger-Huet anomaly was present together with pancytopenia and its related hazardous consequences. As stated above, there was no pancytopenia in our beta-thalassaemic heterozygote with this leucocyte anomaly. According to Saita and Moreo (1959) and Gaultier, de Traverse, Coquelet, Loygue, Housset, and Gervais (1966), the behaviour of the haemopoietic system, including the results of haemoglobin analyses, is no different in beta-thalassaemic heterozygotes with chronic benzene poisoning than those in detected persons suffering from the same disease without the haemoglobinopathy. Contrary to this, Aksoy and Erdem (1969) found a very high level of fetal haemoglobin in two beta-thalassaemic heterozygotes suffering from aplastic anaemia due to chronic benzene poisoning. The investigators have tried to explain the considerable variation in the concentration of HbF encountered in beta-thalassaemic heterozygotes with aplastic anaemia due to chronic benzene poisoning by the theory that different genes are responsible for beta-thalassaemia.

The observations mentioned above, namely, acquired pseudo-Pelger-Huet anomaly and a very high level of fetal haemoglobin in beta-thalassaemic heterozygotes associated with chronic benzene poisoning, lead us to suggest that some forms of beta-thalassaemia increase the deleterious effects of benzene on the haemopoietic system.

Lymphopenia and lymphocytosis Goldwater (1941) has drawn attention to the presence of a relative and absolute lymphopenia in chronic benzene poisoning. In that study an absolute lymphopenia was detected in 28 of 37 workers with leucopenia (75%). In only one worker with leucopenia was a mild absolute lymphocytosis present. In another worker with normal haematological findings, a mild absolute and

relative lymphocytosis was detected together with an eosinophilia of 8%. Bernard (1942) reported a marked or moderate lymphocytosis in several individuals with chronic benzene poisoning. Therefore we are inclined to consider the mild lymphocytosis in two of our workers the result of chronic exposure to benzene.

Eosinophilia In six workers (2.76%) the proportion of eosinophil leucocytes in the peripheral blood was higher than 8%, which was the upper limit of eosinophils in the 100 control subjects apart from one who had 10% eosinophils. In one worker, in whom no clue for the presence of a parasitic infestation including hydatid cysts was found, the eosinophilia was as high as 39%. Three months after the cessation of exposure, eosinophilia had fallen to 13%. In another worker leucopenia was associated with 9% eosinophilia. The mean eosinophil value for 217 workers was 2.75% (SD $\pm$ 0.9). On the other hand, the mean value and standard deviation for the control group were 2.7% ($\pm$ 2.0); for the mean differences between the values of eosinophils of the normal control subjects and of the workers under investigation P was less than 0.9, indicating that there was no significant difference between the values of exposed workers and those of the controls.

Although the presence of eosinophilia due to chronic benzene exposure has been reported by various authors, others have not been able to verify their results. According to Heim de Balzac and Lafont (1910), eosinophilia may be present in individuals with chronic benzene exposure, though no other haematological changes can be observed. Duvoir and Dérobert (1942) have recorded eosinophilia exceeding 5% in 21.8% of the 555 individuals exposed to benzene. In that study the maximum value of the eosinophil count was 18.1%. Similarly, Savilahti (1956) has found eosinophil levels ranging between 6 and 15.5% in 18 of a series of 147 individuals exposed to benzene. On the other hand, Hamilton-Paterson and Browning (1944) and Goldwater (1941) have not encountered eosinophilia in their series. According to our results 2.75% eosinophilia is an inconstant finding of the early stage of chronic benzene poisoning.

Basophilia In two workers the basophil leucocyte count was 3%. In one of them basophilia was associated with a mild eosinophilia of 9%. In the latter the leucocyte count was 4 000/mm³. In both cases, a decrease in the basophil leucocytes to 2% three weeks after the cessation of exposure was recorded. The upper limit of the basophil leucocyte count in normal controls was 2%. The mean basophil count for 217 workers was 0.23% (SD $\pm$ 1.7). For 100 controls it was 0.33% ($\pm$ 1.4). For the mean differences between the values of the normal

control subjects and those of the workers under investigation P was less than 0.2, showing that the difference between the values of the exposed workers and those of the controls was not significant.

An increase in basophil leucocytes was recorded by Smith (1928), though it has not been verified by others (Goldwater, 1941; Savilahti, 1956; Browning, 1965). From our results we would suggest that a mild basophilia may rarely be found in the early stages of chronic benzene poisoning.

Platelets Thrombocytopenia was detected in 20 workers (9.2%). Thrombocytopenia alone was present in only four workers (1.84%). The platelet levels in these individuals ranged between 100 000 and 140 000/mm³ with the direct counting method of Brecher and Cronkite (1950). The *in-vitro* platelet functions, such as spontaneous aggregation and adhesion to glass, viscous metamorphosis, and ADP and distilled water induced aggregation, were normal (Caen and his colleagues, 1966; Balkuv and Ulutin, 1967). The mean platelet count for 217 workers was $417 \times 10^3/\text{mm}^3$ (SD $\pm$ 117.5×10^3). The platelet count for the control group was $514 \times 10^3/\text{mm}^3$ (SD 84.5×10^3). For the mean differences between the values of the normal control subjects and those of the workers under investigation P was less than 0.001.

Apart from that, giant platelets were observed in the peripheral blood of one worker in whom the platelet counts were within normal limits. In this patient, after cessation of exposure, the giant platelets gradually disappeared. In 10 workers (4.6%) an association of thrombocytopenia and leucopenia was detected. The white blood cell counts of these subjects ranged between 2 200 and 3 200/mm³. The range for platelets was between 100 000 and 143 000/mm³.

A decrease in the platelet count, in varying degrees, has been reported in cases of chronic benzene poisoning. According to Savilahti (1956), thrombocytopenia is the most frequent and sometimes the only finding in chronic benzene poisoning. Goldwater (1941), on the other hand, regards thrombocytopenia as being less frequent than anaemia and macrocytosis. Grazioli and Monteverde (1960) reported that thrombocytopenia was not a constant finding in the majority of cases resulting from chronic benzene exposure.

Leucocytosis and leucocytosis associated with thrombocytosis Leucocytosis alone and in association with thrombocytosis was observed in five and two workers, respectively. In one patient each of the former and the latter groups these haematological changes were due to an acute attack of rheumatic fever. Similarly, in two subjects of the former and in one of the latter groups no obvious cause for these

haematological changes could be identified. Also, in two patients with leucocytosis, the finding was transient and disappeared within a few days.

Although the possibility cannot be completely ruled out, it is difficult to attribute leucocytosis and leucocytosis associated with thrombocytosis solely to chronic benzene exposure. Nevertheless the situation may be similar to the effect of some myelotoxic agents, such as nitrogen mustard and cyclophosphamide, which sometimes cause a temporary increase in leucocytes at the beginning of treatment.

Pancytopenia Pancytopenia was detected in six of the 217 workers (2.76%). The interesting point was that pancytopenia had not progressed sufficiently to give rise to signs and symptoms of aplastic anaemia. It was after the detection of aplastic anaemia that the specific treatment was started. In these cases the red blood cells ranged between 2 100 000 and 3 700 000/mm³, PCV between 18 and 36%, white blood cells between 2 100 and 3 800/mm³, haemo-

globin between 6.3 and 10.7 g/100 ml, and platelets between 65 000 and 152 000/mm³. In four of these cases fetal haemoglobin ranged from 3.1 to 16.8%. In only one worker was the haemoglobin F 1.8%.

Haemoglobin and PCV Haemoglobin levels were less than 12 g/100 ml in 72 of the workers (33.1%) and in 71 (32.7%) the PCV was less than 40%. In these workers, associated with low levels of haemoglobin and PCV, the mean corpuscular volume ranged between 86 and 96 μm^3 and never exceeded 100 μm^3 . On the other hand, in these workers the mean corpuscular haemoglobin concentration never exceeded 30%. According to these values, the anaemia, mild or moderate in degree, was not macrocytic and hyperchromic. On the other hand, 23 workers (31% of anaemic individuals) have responded to treatment with oral iron of approximately one and a half months' duration, at the end of which normal haemoglobin and PCV values have been obtained. In 17 of 100 controls the haemoglobin

TABLE 3
RESULTS OF BONE MARROW PUNCTURES PERFORMED IN 11 APPARENTLY HEALTHY WORKERS USING MATERIALS CONTAINING BENZENE

Case	Type of haematological changes	Bone marrow findings			
		Cellularity	Myeloid series	Erythroid series	Megakaryocytes
1	Leucopenia + thrombocytopenia	Normocellular	No change	No change	Present
2	Leucopenia + thrombocytopenia	Normocellular	Maturation arrest	Vacuolization	Decreased in number
3	Leucopenia + thrombocytopenia	Slightly hypocellular	No change	No change	Present
4	Leucopenia + thrombocytopenia	Slightly hypocellular	Maturation arrest	No change	Present
5	Acquired pseudo-Pelger-Huet-anomaly	Hypercellular	Marked maturation arrest	Slight maturation arrest	Present
6	Lymphocytosis	Normocellular	Vacuolization in myelocytes	No change	Present
7	Pancytopenia	Normocellular	Maturation arrest	Maturation arrest	Present
8	Pancytopenia	Normocellular	No change	No change	Present
9	Pancytopenia	Normocellular	Maturation arrest, vacuolization in myelocytes and plasma cells arrest	No change	Present
10	Pancytopenia	Slightly hypocellular	Maturation arrest, vacuolization in myelocytes and plasma cells arrest	No change	Present
11	Pancytopenia	Slightly hypocellular with mild increase in lymphocytes	No change	No change	Present

levels were less than 12 g/100 ml, and in 21 the PCV was less than 40%.

Anaemia, according to Goldwater (1941), is the most frequent finding in chronic benzene poisoning, the decrease in haemoglobin being less than that of the red blood cells. Similarly, Savilahti (1956) has reported the presence of a mild anaemia as a constant finding which was usually hypochromic in type. Browning (1965), on the other hand, has stated that in the early stage of mild chronic benzene poisoning, anaemia may be transient but may gradually increase in severity in proportion to the extent of exposure. Furthermore, Kühböck and Lachnit (1962) did not confirm macrocytosis as an infallible sign of early benzene poisoning.

We found a mild or moderate hypochromic or normochromic anaemia in almost 33% of the 217 workers investigated. The same finding was present in only 21% of the control group. Thus treatment with oral iron was given to some (31%) of the anaemic workers with a resulting disappearance of the anaemia. Therefore, the presence of an iron-deficiency anaemia in association with the finding of chronic benzene poisoning was a possibility, though the effects of chronic exposure to benzene cannot be ruled out completely.

Bone marrow The state of the bone marrow was investigated in 11 workers, four with leucopenia associated with thrombocytopenia, one with lymphocytosis, one with acquired pseudo-Pelger-Huet anomaly, and five with pancytopenia (Table 3). No remarkable changes were observed in two of them. In only one of the remainder was the bone marrow hypercellular with a maturation arrest in the erythroid and myeloid series. In another case, the bone marrow was slightly hypercellular with the arrest of maturation in the granulocytic series. In two workers the bone marrow was normocellular, and in three slightly hypocellular, with maturation arrest in both the erythroid and myeloid series. In another three, the bone marrow showed marked vacuolization.

A great variation in the bone marrow findings has been reported both in animals poisoned with benzene experimentally and in human beings with the signs and symptoms of chronic benzene intoxication (Mallory, Gall, and Brickley, 1939; Browning, 1965; Wintrobe, 1967). The same variation was detected to a lesser extent in the 11 workers in our series in whom features accompanying the early stages of chronic benzene poisoning were present. In the majority of our cases the bone marrow smears were normocellular; in the others they were either hypocellular or hypercellular. Some of them also had a maturation arrest in either the erythroid or myeloid series or in both. In some, the only abnormal finding was the vacuolization detected in the myelocytes or plasma cells (case 9). Furthermore, in two

subjects there was no change in the bone marrow smears in spite of the leucopenia associated with thrombocytopenia or pancytopenia (cases 1 and 8).

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