

THE JOURNAL OF INDUSTRIAL HYGIENE AND TOXICOLOGY

VOLUME 23

JUNE, 1941

NUMBER 6

RECOVERY FOLLOWING EXPOSURE TO BENZENE (BENZOL)*

LEONARD J. GOLDWATER AND MARGARET P. TEWKSBURY

Departments of Preventive Medicine and Clinical Pathology, and Occupational Disease Clinic, New York University College of Medicine, New York City

THE LITERATURE dealing with follow-up studies in non-fatal cases of benzene poisoning is not very extensive. Erf and Rhoads (1) have recently reported on the course of 9 cases of benzene poisoning over periods of from 2 to 5 months following cessation of benzene exposure. These patients all received intensive anti-anemic therapy and all but one recovered. In the extensive review of benzene (benzol) poisoning contained in the British Medical Research Council's report on industrial solvents (2) mention is made of 14 workers who were re-examined following removal from or mitigation of benzene exposure. It is to be re-

gretted that full details concerning these cases are not given.

During the early part of 1938 a study of benzene poisoning in the rotogravure printing industry was undertaken by the Division of Industrial Hygiene of the New York State Department of Labor (3). This study covered 332 persons of whom 130 presented sufficiently marked hematologic abnormality to be considered cases of benzene poisoning. The atmospheric concentration of benzene to which the men were exposed varied from 11 to 1060 p.p.m. and the duration of exposure from 6 to 60 months. A detailed analysis of the blood findings in this investigation has been published elsewhere (4). The use of benzene was discontinued in this industry immediately upon the discovery of the existence of a hazardous situation in April 1938.

The present report deals with three sets of follow-up blood studies. The

* Received for publication February 21, 1941.

Read before the American Industrial Hygiene Association, Pittsburgh, May 9, 1941.

The term "benzene" is employed throughout the Journal.

The Editors.

first covered 56 workers in one printing establishment (designated Plant A) 3 months after cessation of the benzene exposure, the second involved complete blood examinations on 49 employees of a second printing plant (designated Plant B) approximately 14 months after the use of benzene had been discontinued, and the third entailed re-examination of 108 men from Plant A about 3 years after the original studies. At this time 20 men who had entered the employ of this company during the interim were also examined. Arrangements for re-examination of the second and third groups at the Occupational Disease Clinic of the New York University College of Medicine were made by the Division of Industrial Hygiene of the New York State Department of Labor with the cooperation of the employers and the printing pressmen's union representing the workers.

In evaluating the results of the studies reported in this paper it must be borne in mind that other solvents had been substituted for benzene when the use of the latter was discontinued. The several ink manufacturers from whom the printing plants under investigation obtained their inks were extremely co-operative in supplying information as to the nature of the materials that had been used in place of benzene. The great bulk of the solvent material used consisted of various petroleum naphthas covering a boiling range of about 150°F to 300°F. In addition, small amounts of some of the better known esters and ketones were used in certain of the inks.

Mention has already been made of the wide range of vapor concentrations that prevailed during the period of benzene exposure. Inasmuch as no radical changes in ventilation or in operating practice were made follow-

ing the elimination of benzene no great difference in vapor concentrations could have been expected. The few air analyses made confirmed the expected findings. It can be stated with reasonable certainty that the vapor concentrations of the minor constituents of the inks were well below the levels which might be considered toxic.

METHODS

The technics followed in examining the blood were the same as those followed at the time of the original examination (4) and the counts were all done by the same person who made the original determinations. In Plant A the first re-examination was limited to a study of the hemoglobin value, the erythrocyte count and the leucocyte count. For the Plant B group and the second re-examination at Plant A, hemoglobin, red and white count, differential, platelets, hematocrit and the indices of mean corpuscular volume, hemoglobin and hemoglobin concentration were done. As the men reported, they were questioned regarding symptoms and as to what treatment, if any, they had received in the interval between examinations. All but five of the men who were re-examined had remained at work without losing any time. Four of the five were away from their jobs for from 2 to 4 months and the fifth had not returned to work at the end of 14 months.

Re-examinations at Plant A 2 months after cessation of the use of benzene

When the original survey was begun in April 1938 it was necessary to examine a large number of men in a relatively short time. As a rapid "screening" method it was decided to do a hemoglobin determination and a leucocyte count on each worker and more complete studies on those found to

have low values in either of these tests. It subsequently developed that this rapid survey method was entirely unsatisfactory for case finding (3, 4). Re-examinations 2 months later were done on 56 individuals and consisted of hemoglobin, erythrocyte and leucocyte determinations. The group selected for re-examination included 17 cases which had originally been considered definitely abnormal, 16 borderline cases and 23 whose blood pictures had been normal. Because of the limited information obtained at the time of the first examinations, only limited comparisons can be made.

Hemoglobin. 54 cases are available for comparison. The frequency distribution of these cases in April 1936 as compared with June 1938 is shown in table 1. It is apparent that there has been an upward shift of the values, but the change is not very striking. Since relatively few cases had very low hemoglobin values at the time of the original examinations, no great improvement in the group as a whole could have been expected.

Erythrocytes. There were 34 cases in which red cell counts were made on both occasions. As shown in table I, 16 of the 34 had reduced erythrocyte counts (less than 4.5 million) at the time of the first examinations and thirteen still had subnormal counts 2 months later. Actually the mean value was slightly lower at the later date, although the difference is quite insignificant. Furthermore, there were 6 cases in which the second count was lower than the first. Although the comparison has been made on a small group, it seems apparent that it is possible for the erythrocyte count to remain depressed or even to continue to fall for a period of at least 2 months after cessation of benzene exposure.

TABLE 1
COMPARISON OF HEMOGLOBIN, ERYTHROCYTE AND LEUCOCYTE VALUES IN PLANT A
IN APRIL 1938 AND IN JUNE 1938

	APRIL 1938		JUNE 1938	
	Number	%	Number	%
Hemoglobin				
GM. PER 100 CC.				
10.0-10.9	2	3.7	0	0
11.0-11.9	2	3.7	1	1.9
12.0-12.9	7	12.9	7	12.9
13.0-13.9	25	46.3	18	33.3
14.0-14.9	15	27.8	19	35.2
15.0-15.9	3	5.6	9	16.7
Total....	54	100.0	54	100.0
	Mean, 13.54 gm. St. dev., 1.05		Mean, 14.02 gm. St. dev., 0.653	
Erythrocytes				
MILLIONS				
3.0-3.4	1	2.9	2	5.9
3.5-3.9	4	11.8	5	14.7
4.0-4.4	11	32.4	6	17.6
4.5-4.9	10	29.4	16	47.1
5.0-5.4	7	20.6	4	11.8
5.5-5.9	1	2.9	1	2.9
Total....	34	100.0	34	100.0
	Mean, 4.559 mil. RBC St. dev., 0.558		Mean, 4.541 mil. RBC St. dev., 0.59	
Leucocytes				
THOUSANDS				
3- 3.9	4	7.1		1.6
4- 4.9	10	17.8	9	16.2
5- 5.9	13	23.2	10	17.6
6- 6.9	9	16.2	11	19.5
7- 7.9	7	12.5	10	17.8
8- 8.9	7	15.5	9	16.2
9- 9.9	2	3.6	1	1.8
10-10.9	4	7.1	1	1.8
11-11.9	0	0	3	5.3
12-12.9	0	0	0	0
13-13.9	0	0	1	1.8
Total.. ...	56	100.0	56	100.0
	Mean, 6.535 St. dev., 2.010		Mean, 6.963 St. dev., 2.040	

Leucocytes. The entire group of 56 cases who were re-examined after 2 months had had leucocyte counts made at the earlier date. As was the case with the hemoglobin values, there had been a slight upward trend, although a considerable number still showed subnormal counts (table 1). In view of the well known lability of the leucocyte count, extended dis-

blood-forming organs caused by benzene can continue to progress for at least 2 months after exposure has ceased. The possible role of the new solvents used has been mentioned and will be discussed briefly later.

Treatment. Some form of anti-anemic therapy was taken by 17 of the workers in Plant A who were re-examined. Of these, 11 had been classified as positive and 6 as borderline. Of the 11 positives, 4 had become negative at the end of 2 months, 3 had changed to borderline and 4 remained positive. At the same time 5 of the 6 borderline cases became positive. In most instances the treatment consisted of liver extract given parenterally two or three times a week, whole liver in the diet twice a week, and some concentrated form of the vitamin B complex taken daily by mouth.

The number of cases involved was not large enough to justify detailed comparison of treated and untreated cases. Actually the proportion of positive and borderline cases who did not receive treatment and showed improvement was practically the same as for the treated group.

Re-examinations at Plant B 14 months after cessation of the use of benzene

The group studied consisted of 49 of the 69 printers who were examined at the time of the original survey. The candidates for re-examination were self-selected in that the same opportunity for examination was presented to all the men, to be accepted on a purely voluntary basis. That this method of selection resulted in a truly representative sample is demonstrated in table 3.

A comparison of the original and follow-up blood studies in the 49 men who were re-examined can best be

TABLE 2

COMPARISON OF STATUS OF CASES IN APRIL 1938 AND IN JUNE 1938, PLANT A
Single abnormalities were used as a basis for classification

APRIL 1938		JUNE 1938 STATUS		
Status	Total	Posi- tive	Border- line	Nega- tive
Positive	17	8	4	5
Borderline	16	6	7	7
Negative	23	2	7	14
Total	56	16	14	26

criteria

Positive :

R.B.C. 4 million or less
W.B.C. 5,000 or less

Borderline:

R.B.C. 4.01-4.50 million
W.B.C. 5-6,000

ussion of these findings does not seem warranted.

Diagnosis. An analysis of the diagnosis of the 36 individuals who were re-examined at the end of 2 months is given in table 2. It is apparent that there had been little change when one considers the entire group. It is true that 9 of the 17 who were originally classified as positive had moved into the borderline and negative groups, but on the other hand 6 borderline and 9 negative cases showed definite regression. This further emphasizes the point that damage to the

made' by considering separately the different blood tests. The results are given in table 4. Those individuals who did not report for re-examination are omitted from consideration.

Hemoglobin. Diminution in hemoglobin values was not a common finding at the time of the 1933 survey. This being the case, no great change in the hemoglobin picture would be anticipated after cessation of benzene exposure. Inspection of the table reveals that there is a slight general shift of the hemoglobin values to a

TABLE 3

DIAGNOSTIC CLASSIFICATION IN 1938 OF ENTIRE PLANT B COMPARED WITH THAT OF GROUP WHICH CAME FOR RE-EXAMINATION

1938 DIAGNOSIS	ENTIRE GROUP		RE-EXAMINED GROUP	
	No.	%	No.	%
Positive.....	29	42.1	20	40.8
Borderline.....	12	17.4	7	14.3
Negative.....	23	40.5	22	44.9
Total.....	69	100.0	49	100.0

higher level but the mean value increased by only 0.57 gm.

Erythrocytes. Diminution of the red cell count was a prominent feature at the time of the original study with practically one half of the subjects having counts below 4.5 million. General improvement in the erythrocyte picture is reflected in the class frequency distributions as well as in the mean values, shown in table 4.

In spite of the upward trend there is still an appreciable proportion of the cases (24%) having counts below 4.5 million 14 months after the termination of benzene exposure.

Leucocytes. A general improvement in total counts was noted in the follow-up study, as indicated in the table. A single case was found to have

TABLE 4
COMPARISON OF BLOOD FINDINGS IN PLANT
B WORKERS IN APRIL 1938 AND IN
JUNE 1939

	APRIL 1938		JUNE 1939	
	Number	%	Number	%
Hemoglobin				
GM. PER 100 CC.				
11.0-11.9	0	0	1	2.0
12.0-12.9	1	2.0	1	2.0
13.0-13.9	18	36.8	3	6.1
14.0-14.9	21	42.9	24	49.0
15.0-15.9	6	12.2	11	22.5
16.0-16.9	3	6.1	8	16.4
17.0-17.9	0	0	1	2.0
Total.. . . .	49	100.0	49	100.0
	Mean, 14.38 gm. St. dev., 0.99		Mean, 14.95 gm. St. dev., 1.05	
Erythrocytes				
MILLIONS				
3.5-3.9	10	21.8	1	2.2
4.0-4.4	12	26.0	10	21.8
4.5-4.9	17	37.0	9	19.5
5.0-5.4	7	15.2	20	43.5
5.5-5.9	0	0	6	13.0
Total.....	46	100.0	46	100.0
	Mean, 4.50 mil. RBC St. dev., 0.4505		Mean, 5.186 mil. RBC St. dev., 0.52	
Leucocytes				
THOUSANDS				
3.0- 3.9	2	4.1	1	2.0
4.0- 4.9	5	10.2	0	0
5.0- 5.9	10	20.4	4	8.2
6.0- 6.9	10	20.4	7	14.2
7.0- 7.9	10	20.4	13	26.5
8.0- 8.9	6	12.3	11	22.5
9.0- 9.9	2	4.1	9	18.4
10.0-10.9	1	2.0	4	8.2
11.0-11.9	2	4.1	0	0
12.0-12.9	1	2.0	0	0
Total.....	49	100.0	49	100.0
	Mean, 6.949 W.B.C. St. dev., 1.050		Mean, 7.049 W.B.C. St. dev., 1.510	

TABLE 4—Continued

	APRIL 1938		JUNE 1939	
	Number	%	Number	%
Lymphocytes				
%				
10-19	4	8.5	3	6.3
20-29	19	40.4	16	34.0
30-39	19	40.4	23	49.0
40-49	4	5.5	4	8.5
50-59	1	2.2	1	1.2
Total.....	47	100.0	47	100.0
	Mean, 30.53%		Mean, 31.6% lymphs	
	St. dev., 8.46%		St. dev., 7.79%	

Blood platelets

THOUSANDS				
Under 50	4	6.9	0	0
50-99	9	20.0	1	2.2
100-149	15	33.3	18	40.0
150-199	8	17.6	11	24.5
200-249	6	13.3	14	31.1
250-299	2	4.5	1	2.2
300-349	1	2.2	0	0
Total.. ...	45	100.0	45	100.0
	Mean, 139,450 platelets		Mean, 170,450 platelets	
	St. dev., 69,700		St. dev., 46,950	

Mean corpuscular volume

CU. μ				
75-79	0	0	3	6.7
80-84	0	0	3	6.7
85-89	9	20.0	11	24.5
90-94	14	31.2	13	28.8
95-99	5	11.1	9	20.0
100-104	6	13.3	3	6.7
105-109	5	11.1	2	4.4
110-114	5	11.1	1	2.2
115-119	1	2.2	0	0
Total.....	45	100.0	45	100.0
	Mean, 97.62 cu. microns		Mean, 92.61 cu. microns	
	St. dev., 8.74		St. dev., 7.64	

TABLE 4—Concluded

	APRIL 1938		JUNE 1939	
	Number	%	Number	%
Mean corpuscular hemoglobin				
gm GM.				
24-26	0	0	3	6.5
27-29	9	19.5	13	28.3
30-32	17	37.0	20	43.5
33-35	12	26.1	~	15.2
36-38	7	15.1	3	6.5
39-41	1	1.2	0	0
Total....	46	100.0	46	100.0
	Mean, 32.8		Mean, 31.9	
	St. dev., 3.105		St. dev., 2.91	

less than 4,000 white cells, and four more had slightly reduced counts (between 5,000 and 6,000). The individual having the count under 4,000 was the same one whose erythrocytes remained under 4 million, indicating that probably he was still suffering from benzene effect 14 months after cessation of exposure.

Lymphocytes. A relative lymphocytosis is usually mentioned as an important part of the blood picture in chronic benzene poisoning. The group of workers under discussion may be seen (table 4) to have had a normal distribution of lymphocyte percentages at the time of the first examination and again 14 months later. This would seem to indicate that the percentage of lymphocytes in the blood is of no significance in the diagnosis of benzene poisoning or in estimating recovery.

Platelets. A significant reduction in blood platelets was found in nearly one-third of the cases in the original examination. In the follow-up study, a single individual (the same one

mentioned above as having low red and white cell counts) was found to have less than 100,000 platelets. It is apparent from the table that appreciable improvement in the platelet picture had taken place.

Mean Corpuscular Volume. The importance of macrocytosis as evidence of benzene poisoning has been pointed out in recent publications (3, 4). In the present series of cases this hematologic abnormality occupied a prominent position. Generally speaking, cessation of benzene exposure resulted in a more nearly normal cell size, but even after 14 months an appreciable number of cases still had abnormally large erythrocytes. The findings are summarized in the table.

Mean Corpuscular Hemoglobin. The findings in this test parallel those for mean corpuscular volume. The results are given in table 4 and call for no particular comment.

Diagnosis. The classification of the 49 cases as to diagnosis at the time of each examination is shown in table 5. The general improvement in the blood pictures naturally resulted in most of the cases falling into the "negative" group after 14 months of freedom from benzene exposure. On the other hand it cannot be said that there had been universal recovery. Table 5 indicates that 4 of the 20 cases originally diagnosed as positive still remained definitely abnormal and four more of this group had shown only partial recovery. Furthermore, there were 2 men, who were considered to have normal blood pictures at the time of the original examinations, whose counts were definitely abnormal 14 months later and 2 more who had shown regression of a lesser degree. In all, 11 of the 49

cases were further from or no nearer to normal when examined 14 months after cessation of benzene exposure.

Treatment. Only 8 of the cases from Plant B who were re-examined gave a history of having taken treatment: two received liver extract parenterally and orally, four took the extract by mouth only, and two added whole liver to their diet once a week.

TABLE 5
COMPARISON OF STATUS OF CASES IN APRIL 1938 AND IN JUNE 1939, PLANT B
Classification based on single abnormalities

Status	APRIL 1938	JUNE 1939 STATUS		
	Total	Positive	Borderline	Negative
Positive.....	20	4	4	12
Borderline.....	7	1	2	4
Negative.....	22	2	2	18

Criteria

Positive:
R.B.C..... 4 million or less
W.B.C..... 5,000 or less
Plates..... 50,000 or less
R.B.C..... <4.5 million with
M.C.V. >100

Borderline:
R.B.C..... 4.01-4.50 million
with normal
M.C.V.
W.B.C..... 5-6,000

Only one had continued under treatment for the entire 14 month period and most had stopped treatment after 2 or 3 months. The one man who had continued under treatment still had a distinctly abnormal blood picture when re-examined.* There was no indication in these 8 cases that the

*This is the case referred to above as having below 4,000 leucocytes and below 4.0 million erythrocytes.

treatment taken had modified the course of recovery.

Re-examinations at Plant A 24 months after cessation of the work of benzene

The group studied consisted of 108 of the 168 men who were examined at the time of the original survey. As was the case with Plant B, the group was self-selected and was made up of a representative sample of the plant personnel. Complete blood studies were made in all cases at the time of re-examination, although as has been stated, only a small group had been fully studied in the original survey. It is felt that the status of the men in Plant A after a 2 year interval can best be brought out by comparing the results of the 1940 examinations with the 1938 findings in the entire group that had been exposed to benzene in all plants, and also by comparing the 1940 results with those of a control series of workers who had had no unusual occupational exposure. These comparisons are made in tables 6 and 7. It can be seen that with one or two exceptions there is very close resemblance between the control group and the Plant A group in 1940, whereas there are striking differences between the controls and the 1938 benzene group, as has been pointed out in previous publications (3, 4). The findings will be discussed very briefly.

Hemoglobin. As was the case in Plant B, low hemoglobin values were not common at the time of the original studies at Plant A in April 1938, but table 6 shows a general increase in the values with a single case remaining significantly low. Experience has shown that indications of early benzene

poisoning are not likely to manifest themselves by a diminution in hemoglobin content of the blood. Consequently the hemoglobin test cannot be used as a criterion in evaluating recovery. All that can be said concerning the present series of observations is that 3 years after exposure to benzene had ceased, a single case (0.9%) was found to have a low hemoglobin value as compared with 4.7% of subnormal values in 235 cases studied at the time of benzene exposure.

Erythrocytes. In connection with recovery, as reflected in the erythrocyte picture (table 6), there are two features which seem worthy of comment. The fact that six (5.5%) of the workers in Plant A were found to have red cell counts below 4.5 million 2 years after cessation of benzene exposure may indicate that recovery was incomplete in this small group. In view of the high proportion of reduced erythrocyte counts at the time of the first examination in 1938 it would seem reasonable to use this test as a criterion of recovery. A second point of interest in connection with the red cells is the fact that 23 cases (21.2%) had counts above 6 million in 1940 and that 6 of the 23 were above 6.5 million. One might speculate on the possibility of these elevated counts being a reflection of the hyperplastic bone marrow which has been described in connection with benzene poisoning (1,5).

Several cases showed an abnormal amount of basophilic stippling and polychromatophilia, but these findings could not be correlated with either high red or white cell counts. Their presence cannot be explained at present.

TABLE 6

COMPARISON OF BLOOD FINDINGS OF THE ENTIRE BENZENE GROUP IN 1938 WITH THOSE OF THE PLANT A MEN WHO WERE EXAMINED IN 1940 AND WITH A CONTROL GROUP

	BENZENE GROUP, 1938		PLANT A, 1940		CONTROL GROUP, 1938	
	No.	%	No.	%	No.	%
Hemoglobin						
GM. PER 100 CC.						
Less than 11.0	1	0.4	0	0	0	0
11.0-11.9	10	4.3	1	0.9	0	0
12.0-12.9	25	10.5	3	2.8	2	2.4
13.0-13.9	95	40.5	34	31.5	25	30.9
14.0-14.9	75	33.2	32	29.7	40	49.5
15.0-15.9	20	8.6	25	25.9	12	14.8
16.0-16.9	6	2.5	9	8.3	2	2.4
17.0-17.9	0	0	1	0.9	0	0
Total	235	100.0	106	100.0	81	100.0
Mean, 13.87 gm. St. der., 1.07		Mean, 14.56 gm. St. dev., 1.08		Mean, 14.34 gm. St. dev., 0.79		

Erythrocytes						
MILLIONS						
1.5-1.9	1	0.6	0	0	0	0
2.0-2.4	1	0.6	0	0	0	0
2.5-2.9	3	1.9	0	0	0	0
3.0-3.4	3	1.9	0	0	0	0
3.5-3.9	22	13.9	0	0	0	0
4.0-4.4	46	29.0	6	5.5	2	2.4
4.5-4.9	50	31.4	28	25.9	16	19.6
5.0-5.4	29	18.2	33	30.7	33	40.6
5.5-5.9	4	2.5	18	16.7	28	34.6
6.0-6.4	0	0	17	13.7	2	2.4
6.5-6.9	0	0	5	4.6	0	0
7.0-7.4	0	0	1	0.9	0	0
Total	159	100.0	108	100.0	81	100.0
Mean, 4.48 St. dev., 0.67			Mean, 5.44 St. dev., 0.645		Mean, 5.32 St. dev., 0.42	

Leucocytes						
THOUSANDS						
2.0- 2.9	6	1.8	0	0	0	0
3.0- 3.9	16	4.8	1	0.9	0	0
4.0- 4.9	26	7.9	3	1.9	0	0
5.0- 5.9	55	16.5	9	5.3	7	8.6
6.0- 6.9	58	11.5	12	11.1	10	12.4
7.0- 7.9	55	16.5	14	13.0	10	12.4
8.0- 8.9	48	14.6	15	13.3	11	13.6
9.0- 9.9	24	7.2	16	14.9	10	12.4

TABLE 6—Continued

THOUSANDS	BENZENE GROUP, 1938		PLANT A, 1940		CONTROL GROUP, 1938	
	No.	%	No.	%	No.	%
Leucocytes—Concluded						
10.0-10.9	26	7.8	14	13.0	13	16.1
11.0-11.9	7	2.1	8	7.4	3	3.7
12.0-12.9	4		5	4.6	1	1.2
13.0-13.9	3		6	5.5	0	0
14-14.9	2	0.6	0	0	1	1.2
15.0 or more	2	0.6	6	5.5	0	0
Total	332	100.0	109	100.0	81	100.0
	Mean, 7,295 St. dev., 2,368		Mean, 9,260 St. dev., 2,710		Mean, 8,253 St. des., 1,896	
Lymphocytes						
%						
10-19	10	9.9	4	3.7	2	2.4
20-29	41	36.6	21	19.4	10	12.4
30-39	41	36.6	57	52.8	40	49.5
40-49	15	13.4	24	22.2	23	29.3
50-59	5	4.5	2	1.9	5	6.2
60-69	0	0	0	0	1	1.2
Total	112	100.0	108	100.0	81	100.0
	Mean, 31.79 St. der., 9.66		Mean, 35.0 St. der., 7.9		Mean, 35.25 St. dev., 11.65	
Platelets						
THOUSANDS						
Less than 50	12	11.2	0	0	0	0
50- 99	23	21.5	7	6.5	0	0
100-149	31	29.0	27	25.0	9	18
150-199	20	18.7	29	26.6	11	22
200-249	12	11.2	19	17.6	20	40
250-299	6	5.6	14	13.0	8	16
300-349	3	2.8	10	9.2	1	2
350-399	0	0	2	1.9	1	2
Total	107	100.0	108	100.0	50	100.0
	Mean, 137,620 St. dev., 13,970		Mean, 195,250 St. dev., 66,600		Mean, 208,000 St. dev., 48,590	

TABLE 6—Concluded

	BENZENE GROUP, 1938		PLANT A, 1940		CONTROL GROUP, 1938	
	No.	%	No.	%	No.	%
Mean corpuscular volume						
CU. μ						
70- 74	1	0.9	9	8.3	7	9.3
75- 79	2	1.9	17	15.5	9	12.0
80- 84	9	8.8	18	16.7	19	25.4
85- 89	19	18.5	27	25.0	20	26.7
90- 94	24	23.2	20	18.5	13	17.3
95- 99	15	14.6	10	9.2	3	4.0
100-104	16	15.5	4	3.7	4	5.3
105-109	5	7.8	2	1.9	0	0
110-114	7	6.0	1	0.9	0	0
115-119	2	1.9	0	0	0	0
Total.....	103	100.0	108	100.0	75	100.0
	Mean, 95.51 St. dev., 9.40		Mean, 88.14 St. dev., 8.58		Mean, 85.30 St. dev., 7.11	
Mean corpuscular hemoglobin						
MG GM.						
20-23	0	0	10	9.2	0	0
24-26	12	10.0	36	33.3	30	41.2
27-29	31	25.8	41	38.0	34	46.5
30-32	40	33.3	17	15.8	9	12.3
33-35	21	17.5	3	2.8	0	0
36-38	11	9.2	1	0.9	0	0
39-41	5	4.2	0	0	0	0
Total	120	100.0	106	100.0	73	100.0
	Mean, 31.6 St. dev., 3.76		Mean, 27.66 St. dev., 2.96		Mean, 9.16 St. dev., 2.02	
Mean corpuscular hemoglobin concentration						
%						
24-26	0	0	0	0	1	1.2
27-29	2	1.9	11	10.2	5	6.1
30-32	40	38.0	72	66.7	55	67.9
33-35	53	50.6	24	22.2	19	23.6
36-38	9	8.6	1	0.9	1	1.2
39-41	1	0.9	0	0	0	0
Total	105	100.0	106	100.0	81	100.0
	Mean, 33.63 St. dev., 2.07		Mean, 31.92 St. dev., 1.75		Mean, 32.02 St. dev., 1.48	

unless they are considered to be further evidence of marrow hyperplasia.

Leucocytes. It can be seen in table 6 that only 3 cases (2.8%) still had significantly reduced leucocyte counts in 1940. These three can probably be considered cases of incomplete recovery. The interpretation of the fact that 17 cases (15.6%) had counts above 12,000 is difficult unless it is on the same basis of bone marrow hyperplasia that has been suggested as an explanation for the high erythrocyte

speculation is the fact that unusually high red and white cell counts were not found in any of the 49 men of Plant B who were examined 14 months after cessation of benzene exposure.

Lymphocytes. The fallaciousness of the idea that relative lymphocytosis is a characteristic feature in benzene poisoning has been pointed out previously in this paper as well as elsewhere (3, 4). The data in table 6 emphasize the fact that relative lymphopenia is likely to occur as a result of exposure to benzene and that following recovery the percentage of lymphocytes tends to increase. The close correspondence between the Plant A group in 1940 and the control group is apparent.

Blood Platelets. Although there had been a general improvement in the platelet picture between 1938 and 1940, there were still 7 cases (6.5%) that might be considered subnormal or incompletely recovered (table 6).

Mean Corpuscular Volume (M.C.V.). In the original studies in 1938 an increase in the average cell size was found to be a very prominent feature. This determination along with the erythrocyte count was shown to be a reliable index of early benzene poisoning. The 1940 follow-up studies revealed that in most cases the cells were normal in size, but that in a few instances macrocytosis persisted. The fact that the average M.C.V. of the 1940 series is significantly larger than that of the control group suggests that there had been incomplete recovery as far as this abnormality was concerned (table 6).

Mean Corpuscular Hemoglobin (M.C.H.) and Mean Corpuscular Hemoglobin Concentration (M.C.C.). At the

TABLE 7
COMPARISON OF SERUM BILIRUBIN VALUES
OF THE ENTIRE BENZENE GROUP IN 1938
WITH THOSE OF 45 CONSECUTIVE CASES
FROM PLANT A IN 1940

SERUM BILI- RUBIN, MG. %	BENZENE GROUP, 1938		PLANT A, 1940	
	No.	%	No.	%
<0.75	69	67.6	33	73.3
0.75-1.0	22	21.6	9	20.0
>1.0	11	10.8	3	6.7
Total.....	102	100.0	45	100.0

counts. It seems worth while pointing out that the mean erythrocyte count for the 17 cases showing leucocytosis was 3.91 million while the mean leucocyte count for the 33 cases having more than 6 million red cells was 10,790. Both of these mean values are significantly higher than those for the entire group. The elevation cannot be accounted for on the basis of hemoconcentration since the hematocrits showed normal cell-plasma ratios. On the other hand, there was no constant elevation in blood platelets in these cases, nor was there an increase in the percentage of polymorphonuclear cells. A further point, inviting

time of the original studies in 1938 there was found to be an increase in M.C.H. values due mainly to the increased cell size, but in part to actual hemoglobin concentration. Inspection of table 6 reveals a general return to normal of the values in these tests with 4 cases showing persistence of a high M.C.H.

Serum Bilirubin. Comparison of the results obtained in 1938 with those of 1940 (table 7) shows that there has been little change in the proportion of low and high values. The findings seem to indicate that the serum bilirubin test cannot be used as a reliable index of benzene poisoning or of recovery.

Diagnosis. Inasmuch as complete blood studies were made on only a small fraction of the Plant A personnel in 1938, there is no way of knowing the number of positive, negative and borderline cases at that time. Using the same criteria that were applied to Plant B, (see table 5), the re-examinations in Plant A in 1940 revealed that 4 of the 108 cases still remained in the positive group and 8 fell into the borderline class. These findings suggest that damage due to benzene may persist for a period of at least 2 years after cessation of exposure. It is interesting to note that two of the cases classified as positive in 1940 had been considered normal in 1938 on the basis of a white cell count and hemoglobin determination. It is possible that if complete blood studies had been done at the time of the first examination in 1938, these 2 cases might have been found to be abnormal at that time.

Symptoms. At the time of the original examinations the workers in

Plant A had many more complaints than those of Plant B (3). This may have been related to the generally higher concentrations of benzene vapor in the air of Plant A. When an attempt was made to correlate symptomatology with blood findings it became apparent that there was no relationship. Many individuals with normal blood had numerous complaints, and many with marked hematologic abnormality had no complaints whatsoever. In view of the fact that the men continued to work in an atmosphere which was laden with solvent vapors, even though benzene was no longer present, it is not surprising that a large proportion continued to have the same complaints that they had before benzene was eliminated. At the time of re-examination there was no correlation between symptoms and blood picture.

New Employees. Mention was made at the beginning of this paper of the fact that 20 men who had entered the employ of Plant A subsequent to the time of the 1938 studies reported for examination in 1940. The employment period for this group varied from 7 to 22 months. Two of these men had erythrocyte counts below 4.5 million associated with mean corpuscular volume values of more than 100 cu. μ and consequently were considered abnormal. One case had a leucocyte count of 21,000 with a normal differential count and another had an erythrocyte count of 6.92 million. Otherwise the blood findings in this group were entirely within normal limits. Interpretation of these abnormalities will be possible only after subsequent observations.

COMMENT

When an attempt is made to analyse the findings in these follow-up studies it is not once apparent that the data are not as complete as might be desired. In dealing with groups of printers actively engaged in pursuing their trade it is obviously not possible to make the detailed observations which can be made on hospitalized patients or on laboratory animals. The difficulties inherent in this type of investigation no doubt explain to some degree the paucity of reports dealing with recovery from benzene poisoning.

In spite of the limitations of the present study there are several findings which throw a certain amount of light on the subject of recovery following protracted exposure to benzene fumes. In Plant A, where the interval between cessation of benzene exposure and the first re-examination was about 2 months there was practically no change in the status of the group studied at the end of this time. The treatment which individuals in group received seemed to have no effect in hastening recovery. As a matter of fact, in a number of cases the blood picture was further from normal after 2 months of treatment than it had been at the time benzene exposure ceased and treatment was begun. This finding suggests that the deleterious action of benzene may continue to operate for several months after the termination of exposure. The possibility of the benzene substitutes contributing to this adverse trend cannot be excluded, but seems extremely unlikely in view of subsequent events.

The workers in Plant B who were examined after an interval of 14 months showed very decided improvement, but not universal recovery. Of particular interest is the fact that 2 individuals whose blood was normal at the time of the first examination had distinctly abnormal findings when re-examined. Both cases exhibited a fall in the red cell count and a concomitant increase in erythrocyte size. 4 additional cases originally classified as positive still remained in a definitely abnormal state and 1 borderline case showed regression.

In Plant A, 4 of the 108 men who were re-examined after 2 years showed distinctly abnormal blood pictures and 8 others exhibited abnormalities of a lesser degree. It thus becomes apparent that it is possible for the effects of benzene to persist for a period of at least 2 years.

The cases which showed regression after the cessation of exposure are somewhat difficult to explain. It would seem that if the solvents which replaced benzene were responsible for the adverse trend, many more cases would have been affected. The much over-worked explanation of "individual susceptibility" does not seem adequate. It is unreasonable to assume that benzene continued to act for a period of 2 years after exposure was terminated. Until further observations can be made on this and on similar groups of workers, one can only speculate as to why a few cases seem to have retrogressed.

SUMMARY AND CONCLUSIONS

1. Three sets of follow-up blood studies were made on roto-gravure printers who had been exposed to

benzene. The studies were made 2, 14 and 24 months, respectively, after cessation of benzene exposure.

2. The studies made on 56 men at the end of 2 months indicated that the toxic effects of benzene may continue to act for a period of at least 2 months following the termination of contact.

3. The studies made on 49 men at the end of 14 months showed that while a large majority of the affected workers had apparently recovered, a small number had failed to regain a normal hematologic status.

4. The studies made on 108 men at the end of 24 months showed that 4

individuals still had distinctly abnormal blood pictures. This indicates that damage to the blood caused by benzene may persist for at least 2 years following cessation of exposure.

5. Recovery is manifested primarily by increase in erythrocyte numbers, decrease in erythrocyte size and increase in blood platelets.

6. The total leucocyte count and the differential formula is an unreliable index of benzene poisoning or of recovery.

7. The usual forms of anti-anemic therapy seem to have no effect in hastening recovery.

BIBLIOGRAPHY

1. ERF, L. A., AND RHOADS, C. P.: The hematological effects of benzene (benzol) poisoning. *THIS J.*, **21**, 421 (1939).
2. Toxicity of industrial organic solvents. Medical Research Council Industrial Health Research Board. H. M. Stationery Office, London, 1937.
3. GREENBURG, L., MAYERS, M. R., COLDWATER, L. J., AND SMITH, A. R.: Benzene (benzol) poisoning in the rotogravure printing industry in New York City. *THIS J.*, **21**, 395 (1939).
4. GOLDWATER, L. J.: Disturbances in the blood following exposure to benzol. *J. Lab. Clin. Med.*, **26**, 957 (1941).
5. MALLORY, T. B., GALL, E. A., AND BRICKLEY, W. J.: Chronic exposure to benzene (benzol). III. The pathologic results. *THIS J.*, **21**, 355 (1939).