AN ENQUIRY INTO THE RELATIVE TOXICITY OF BENZENE AND TOLUENE.

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(With Plates VIII and IX containing Figs. 1–16 and Figs. I–VII in the Text.)

CONTENTS.

I. Introduction.

This clinical and experimental investigation into the relative toxicity of benzene and toluene, more frequently called benzol and toluol, arose out of the examination of a patient whose symptoms, if they are to be taken as due to his occupation, seemed clearly to be attributable to the action of toluene. It may be well to state at the outset that even if we have satisfied ourselves of the *causa causans* in this case, it does not carry with it the implication that toluene is a dangerous trade solvent. A perusal of the literature of this subject and our own experiments on animals would suffice to convince us of the variability of action of these substances, of the contradictory statements and results which are put forward with regard to them, of their extreme selectiveness and minority action, of the existence now of stimulating and now of depressing actions presumably dependent on dosage, and of the non-specific or non-pathognomonic character of the so-called typical symptoms. The questions too of the establishment of tolerance to a poison is one the meaning of which has not been sufficiently investigated. An increased and not a lessened resistance may perhaps, in some cases, be developed with long-continued exposure to poisonous action. Alcohol is a poison, but its long-continued use in diluted amount may lead to no serious poisoning. The same may be said of the alkaloids theine and caffeine. Opium in certain doses may be a stimulant and strengthen resistance to adverse conditions, while on the other hand it is a

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powerful narcotic and can be lethal. Again, one endeavours in experimental work to accelerate the result by the use of appropriate animals, appropriate doses and appropriate methods of administration. The idea is that the results thus conveniently and quickly obtained may be applicable *mutatis mutandis* in a type of case—the human case—which otherwise differs from the experimental cases in important respects.

The special subject of our investigations may be considered under the headings: (1) Historical survey; (2) Data collected or observed; (3) Laboratory experimentation on animals; (4) Examination of workers using benzene or benzene homologues; (5) Clinical and pathological description of a case of aplastic or, as the case may be, agranulocytic anaemia in a worker exposed to toluene vapour; (6) Discussion and summary; (7) Conclusion.

It is necessary, however, to emphasise the partial nature of our investigation, which we may hope will be continued, particularly on statistical, large-scale lines.

II. Historical survey.

Apparently the first description of chronic as distinct from acute benzene poisoning to be published was by Santesson (1897) and the first case in America by Selling (1911). Animal experimentation on this subject was initiated by Lehmann (1909–10). But the really important publication on the subject of benzene poisoning is that of Selling (1911, 1916), who did a large series of experiments on animals and who considered not merely the toxic effects of benzene but the very important subject of recovery from these effects and the regeneration of the injured tissues after removal from its influence. The thoroughness with which this work was carried out leaves little to be desired in the way of detail. His injection of benzene subcutaneously brought out, (1) the rapid leucopenia, (2) a far less obvious effect on erythrocytes, (3) a stimulating effect on the bone marrow cells in the early stages, and (4) a cell destruction in the later stages. These effects have only been partially confirmed in our experiments with animals. One statement made by Selling, on which we place great stress and which has scarcely received any attention, is that "in general the response of the bone marrow is not specific. It does not respond to a loss of white blood cells solely by the production of granulocytes nor to the loss of red blood cells solely by the production of erythroblasts." As Schridde (1908) points out "the regeneration of the blood seems independent of the needs and in the individual case it is hard to prophesy just what proportion of granulocytes and erythrocytes will be found." The subject of benzene poisoning has received, comparatively speaking, much attention and the literature is fairly plentiful. That is not the case for the higher homologues of benzene—toluene, a monomethyl substitute and xylene, a di-methyl substitute. The various positions at present taken up with regard to toluene are that it is (1) distinctly less toxic than benzene, (2) in some respects more toxic, and (3) that it has special characteristics which differentiate its toxicity from that of benzene. Thus Selma Mayer (1931) considered that the homologues of benzene

bring about similar changes in the blood cells and that a relative lymphocytosis was characteristic not only of benzene but also of toluene and other substances. Adler-Herzmark and Selinger (1930–1) refer to the relatively large number of morphologically changed erythrocytes and the frequent occurrence of anisocytosis and poikilocytosis in xylene and toluene poisoning as compared with benzene. Batchelor (1927) explicitly investigated the question in which we are interested, that of the relative toxicity of benzene and its higher homologues. He enters fairly fully into the opinions already held or promulgated on this subject. His judgment may be summed up in the statement that "there seems to be considerably less hazard connected with toluol administration from the clinical, the immunological and the pathological aspects." The rapid appearance of symptoms, their severity and their relatively rapid disappearance are in accordance with the lower boiling-point, the greater volatility and the lower molecular weight of benzol as compared with the homologue substances, which are used industrially in place of it. The chief differences which Batchelor and others seem to have found between benzene and toluene or xylene, for doses of each that are capable of producing symptoms of poisoning, are that benzene acts as a convulsive neurotoxin and then as a narcotic, whereas the latter, while also narcotic, does not produce the same amount of neuro-irritation. All three substances may be regarded as having a destructive effect on the entire haemopoietic system, but from the toxic standpoint toluene and xylene, as actually used in industry, are vastly superior to benzene. On the other hand Batchelor seems to ascribe a more dangerous action to toluene than to benzene in acute poisoning. Stocke (1929), describing what he specifically calls acute poisoning by xylene and toluene, is insistent on the dangerous action of these substances in certain types of colour-printing processes. The workers dealt with by him were selected for examination as showing definitely the effects of poisoning, and his main findings were that the effect of toluene and xylene on the haemopoietic system is expressed in a quite definite relative lymphocytosis, that in slight affections there is a slight increase in the number of leucocytes and a fall in severe cases and that there is no anaemia. Lehmann (1909–10) too found in animals that toluene and xylene while giving rise to less convulsive spasm produce a more rapid narcosis than benzene, and that recovery—possibly because of slower elimination—was slower than with benzene. Rambousek (1911) argued for the less toxicity of toluene. An important article in the literature of this subject is that already referred to by Adler-Herzmark and Selinger (1930–1). In this they state their opinion that although the small toxicity of the higher homologues of benzene may appear to be evident by animal experimentation the question, so far as the human subject goes, still remains somewhat of an open question. That these homologues are injurious to the blood-forming organs they maintain is proved by their own work, but it is more difficult to say whether under normal working conditions these substances are less toxic than benzene.

Selling (*loc. cit.*) in his experimental work deals very fully with the question

of regeneration. In some experiments by Weiskotten, Gibbs, Boggs and Templeton (1919–20) it would appear that to some degree the leucopenia produced by inhalation of benzene on rabbits may be permanent. The variability of effect of a poison like benzene is constantly being referred to by workers on the subject. Its selective action on certain individuals in whom the reaction may be looked on as an idiosyncrasy is put forward by many writers. "The victims...always constitute a small minority of the workers; in many cases...a single individual may contract fatal poisoning in an environment that does not give rise even to mild poisoning in the others" (Alice Hamilton, 1931). This statement seems to us to put the matter very clearly, to be applicable to experimental results as well as industrial cases and to be capable of expansion to account for variation in type of result, for tolerance and even for total immunity. It also applies to the effects of poisoning as seen in the organs of the body. It may be that the higher homologues of benzene should be regarded as drugs which are essentially stimulating to the bone marrow, for example, except after very prolonged action when—we may suppose—exhaustion would necessarily succeed to a period of long-continued and excessive activity. Mitnik and Genkin (1931) say that in the poisoning of animals with small doses of benzene itself Selling, Robe and Hirschraud, Langlois and Desbouis, and others found a leucocytosis and erythrocytosis to begin with. These are stimulant effects. In this article by Mitnik and Genkin we also find the statement that Pappenheim (1914) would attribute the action of benzene to its capacity to dissolve lipoids. "If it were correct," says Woronow (1929), "that the benzol owes its action to its fat-dissolving power then other substances with this action should bring about the same condition. Such a substance would be xylol which indeed is a better solvent of fat than benzol." "As a rule in injection of xylol the number of leucocytes fell during the first 4 to 5 days, then began definitely to rise and reached by the 9th or 10th day quite high values—up to 20 to 30,000. With some variations from day to day these values remained up to the end of the research." With benzene there was a fall in the leucocytes, then, after a short rise, a complete disappearance shortly before death.

Englehardt's (1931) work, although it is rather divergent from that with which we are immediately concerned, is instructive because it affords an insight into the close parallelism, that is to say the non-specificity, existing between the action of many industrial poisons. He was occupied with a comparison of the effects of benzine and benzene and found considerable similarity between these two different types of chemical solvent. This is brought out also from the work of Hertzmann (1931) on the histological features of poisoning by the same two substances. Evidently a useful measure of relative toxicities of these various poisons would be the concentrations necessary for the production of equal symptomatic effect. This was done for example in a comparison of benzine and benzene by Fuhner (1921) for one symptom. The isonarcotic doses of these substances are given in milligrammes per litre of air for pentan, hexan

and heptan, which are components of benzine, as 377, 147 and 64 respectively and for benzene as 38.

An important finding, at least for the guidance of examiners of industrial workers, is that of the American Committee on Benzol, Chemical and Rubber Sections, National Safety Council Final Report (1926) who express it as their opinion that the worker should be withdrawn from exposure when it is found that he has a leucocyte count under 5000 per c.mm. or haemoglobin below 70 per cent. and erythrocytes down by 25 per cent. Jerome Mayers (1928) lays down that leucocyte values under 6450 are pathological for blood taken from the ear, and under 5600 for blood from the finger. Adelaide Ross Smith (1928) summarises the pathological blood picture in benzene poisoning as: anaemia, leucopenia, the presence of abnormal cells such as myelocytes and Turck's irritation cells, and an abnormal increase in endotheliocytes. The risk of poisoning was not limited to those who worked directly with benzene; but workers who were... merely working in rooms where benzol was used were also subject to its effects. Another point in the blood picture which is from time to time mentioned and which we believe may be real is the moderate degree of eosinophilia (Selma Meyer, 1931). Adler-Herzmark and Selinger, Meyer, and Stocke seem to be more or less united in thinking that the relative lymphocytosis apparent among workers is greater among those using xylene and toluene or combinations of these than with benzene alone. A remark made by Wurm (1931) is one which we think may possibly explain some of the difference of action between benzene and its higher homologues. It is to the effect that the smallness of the injury induced by the higher homologues is merely due to their less volatility. With a sufficiently long action toluene can be likewise harmful in its effects. The boiling-points of these three substances is given by Zangger (1930) as 80, 110 and 140° C. respectively.

Mention may be made here, as it has a bearing on the particular clinical case we are describing, of the remark of Jaffe (1932) that "in spontaneous or experimental agranulocytic conditions inflammation is characterised by the severity and the predominance of the alterative process and the lack of cellular response," and that histiocytes and lymphocytes are unable to compensate for the loss of granulocytes.

An important endeavour to connect the clinical constitution of substances related to benzene with toxicity is to be found in the work of Chassevant and Garnier (1903). They set out to determine the modification in the toxic properties of the benzene ring with substitution of different radicals for one or more of its hydrogen atoms. According to these authors monosubstituted derivatives such as toluene (methyl benzene) and ethyl benzene are more toxic than benzene itself and always more than bisubstituted derivatives such as the xylenes. Among the xylenes the para-derivative is more toxic than the meta- and the meta- than the ortho-. They found that the addition of the single methyl radical CH_3 augments the toxicity of the benzene nucleus as also does the radical OH, whilst the radical COOH diminishes it.

The position with regard to benzene and toluene, as it is at present, may be summed up in the words of Henderson and Haggard: "In the literature the relative toxicity of benzene and toluene is uncertain. Probably there are no great differences in (acute) toxicity.... Toluene is less active than benzene in causing chronic poisoning."

III. Data collected or observed respecting (*a*) toluene and (*b*) benzene.

The most important data which we have been able to obtain, dealing with the effect of benzene, toluene and xylene upon industrial workers themselves, are those of Adler-Herzmark and Selinger (1930). These are set out in three tables with great detail, individual by individual, and we have endeavoured to extract some of the facts which they demonstrate. Those which we have chosen as especially interesting are the effect of toluene and of benzene respectively on the erythrocyte count, the leucocyte count, and the polymorph percentage, with duration of exposure. We have also assembled tables of symptoms under the two headings benzene effects and toluene effects.

(*a*) *Toluene.*

Tables I–III record the effects on erythrocyte and leucocyte total counts and the polymorphonuclear relative percentage with years of exposure. Males 31, females 15. 1 year = 0–1 but under 1, and 2 years = 1–2 but under 2.

Mean duration of exposure (ungrouped data), including case of 23 years = 4·1 years and excluding this case = 3·6 years.

Table I.

Erythrocytes (millions)	Duration of exposure in years: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Totals
2·5 (2–3)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	No observation of red blood cells for case of exposure for 23 years.						0
3·5 (3–4)	3	3	1	.	.	.	.	1	2	.	1	.	.	.	.	.	1							12
4·5 (4–5)	6	2	7	3	2	2	.	2	.	1	2	.	.	.	.	.	.	Mean from ungrouped data						27
5·5 (5–6)	.	3	.	1	.	2	.	.	.	.	.	.	.	.	.	.	.							6
6·5 (6–7)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4,400,000						0
Totals	9	8	8	4	2	4	0	3	2	1	3	0	0	0	0	0	1	0	0	0	0	0	0	45

Table II.

Leucocytes (thousands)	Duration of exposure in years: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Totals
3·5 (3–4)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
4·5 (4–5)	.	.	1	1	.	.	.	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	1	5
5·5 (5–6)	1	2	.	1	.	1	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	6
6·5 (6–7)	1	1	.	.	.	.	.	1	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.	5
7·5 (7–8)	3	3	3	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	11
8·5 (8–9)	2	1	1	.	1	1	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	7
9·5 (9–10)	.	1	2	.	1	1	.	.	.	2	.	.	.	.	.	.	.	.	.	.	.	.	.	7
10·5 (10–11)	.	.	1	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
11·5 (11–12)	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
12·5 (12–13)	1	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
13·5 (13–14)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
Totals	9	8	8	4	2	4	0	3	2	1	3	0	0	0	0	0	1	0	0	0	0	0	1	46
Means	8·4	7·3	8·1	6·3	9	7·8	.	7·2	5·5	.	8·5													

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Table III.

Polymorphs %	Duration of exposure in years: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Totals
51	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
52	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
53	.	.	1	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	1	3
54	.	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
55	1	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
56	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
57	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
58	.	1	1	1	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4
59	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
60	2	1	.	.	.	.	.	.	.	.	1	.	.	.	.	.	1	.	.	.	.	.	.	5
61	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	1
62	.	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
63	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
64	.	.	.	.	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
65	.	1	2	.	.	1	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	5
66	1	.	.	.	.	.	.	1	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.	4
67	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
68	3	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4
69	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
70	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
71	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
72	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
73	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
74	.	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
75	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
76	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
77	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
78	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
Totals	9	8	8	4	2	4	0	3	2	1	3	0	0	0	0	0	1	0	0	0	0	0	1	46
Means	63	64·1	67·3	61	63·5	61	.	60·3	65·5	.	59·7													

(*b*) *Benzene.*

Tables IV–VI the effects on erythrocyte and leucocyte total counts and the polymorphonuclear relative percentage with years of exposure. Males 15, females 22.

Table IV.

Erythrocytes (millions)	Duration of exposure in years: 1	2	3	4	5	6	7	8	9	10	11	12	13	Totals
2·5 (2–3)	.	.	.	.	.	.	.	.	.	.	.	.	.	0
3·5 (3–4)	.	.	4	1	1	1	.	1	.	.	1	.	1	10
4·5 (4–5)	2	2	2	5	3	4	2	.	2	.	.	.	1	23
5·5 (5–6)	.	.	2	.	.	1	1	.	Mean from ungrouped data:					4
6·5 (6–7)	.	.	.	.	.	.	.	.	4,300,000					0
Totals	2	2	8	6	4	6	3	1	2	0	1	0	2	37

The symptoms associated with exposure to the vapour of benzene or toluene are manifold and referable to more than one of the systems. It is not easy to obtain a complete or even a true record of symptoms, as so much depends on the view taken by the worker of the examination to which he is being subjected. For that reason an objective examination like that of the blood, which may perhaps with truth be regarded as a general, if not very specific, indicator of ill health, is very valuable. In the series of workers dealt

Table V.

Leucocytes (thousands)	Duration of exposure in years 1	2	3	4	5	6	7	8	9	10	11	12	13	Totals
3·5 (3–4)	.	.	.	.	.	.	.	.	.	.	.	.	.	0
4·5 (4–5)	.	.	.	1	.	2	1	.	.	.	.	.	.	4
5·5 (5–6)	.	.	1	.	2	1	.	1	1	.	.	.	1	7
6·5 (6–7)	1	.	1	1	.	1	.	.	.	.	1	.	1	6
7·5 (7–8)	.	.	2	1	1	1	1	.	.	.	.	.	.	6
8·5 (8–9)	.	2	.	1	.	.	.	.	.	.	.	.	.	3
9·5 (9–10)	.	.	3	1	.	.	1	.	1	.	.	.	.	6
10·5 (10–11)	.	.	.	.	1	1	.	.	.	.	.	.	.	2
11·5 (11–12)	.	.	.	1	.	.	.	.	.	.	.	.	.	1
12·5 (12–13)	.	.	1	.	.	.	.	.	.	.	.	.	.	1
13·5 (13–14)	1	.	.	.	.	.	.	.	.	.	.	.	.	1
14·5 (14–15)	.	.	.	.	.	.	.	.	.	.	.	.	.	0
Totals	2	2	8	6	4	6	3	1	2	.	1	.	2	37
Means	10	8·5	7·3	8	7·3	6·5	7·2	5·5	7·5	.	6·5	.	6	

Table VI.

Polymorphs %	Duration of exposure in years 1	2	3	4	5	6	7	8	9	10	11	12	13	Totals
42	.	.	.	.	1	.	.	.	.	.	.	.	.	1
45	.	.	.	1	.	.	.	.	.	.	.	.	.	1
50	.	.	1	.	.	.	.	.	.	.	.	.	.	1
54	.	.	.	.	.	.	.	1	.	.	.	.	.	1
55	.	.	.	.	.	.	.	.	.	.	.	.	.	0
56	.	.	1	.	.	.	.	.	.	.	.	.	.	1
57	.	.	.	1	.	.	.	.	.	.	.	.	.	1
58	.	.	.	.	.	1	.	.	.	.	.	.	.	1
59	.	.	.	.	.	.	1	.	1	.	.	.	.	2
60	.	1	1	.	.	.	.	.	.	.	.	.	.	2
61	.	1	1	.	.	1	.	.	.	.	.	.	.	3
62	.	.	1	.	2	.	.	.	.	.	.	.	.	3
63	.	.	.	.	.	.	1	.	.	.	.	.	.	1
64	.	.	.	.	.	.	.	.	.	.	.	.	.	0
65	.	.	1	.	.	2	.	.	.	.	.	.	.	3
66	.	.	.	1	.	.	.	.	1	.	1	.	1	4
67	.	.	.	.	.	.	.	.	.	.	.	.	.	0
68	.	.	.	.	.	.	1	.	.	.	.	.	.	1
69	.	.	.	.	.	.	.	.	.	.	.	.	.	0
70	1	.	1	.	.	.	.	.	.	.	.	.	.	2
71	.	.	.	.	.	.	.	.	.	.	.	.	1	1
72	.	.	.	1	.	.	.	.	.	.	.	.	.	1
73	.	.	.	.	.	1	.	.	.	.	.	.	.	1
74	.	.	1	.	.	.	.	.	.	.	.	.	.	1
75	.	.	.	2	1	.	.	.	.	.	.	.	.	3
76	1	.	.	.	.	.	.	.	.	.	.	.	.	1
77	.	.	.	.	.	1	.	.	.	.	.	.	.	1
Totals	2	2	8	6	4	6	3	1	2	0	1	0	2	37
Means	73	60·5	62·3	65	60·3	66·5	63·3	.	63·5	.	.	.	68·5	

with here we have extracted as typical symptoms, headache, cough, giddiness and vomiting with the result shown in Table VII.

Table VII.

	Headache	Cough	Giddiness	Vomiting	Numbers examined
Benzene	11	5	4	4	37
Toluene	12	7	4	5	46

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If leucopenia and anaemia develop with length of exposure to either toluene or benzene, it is not very well brought out by these tables. A leucopenia is certainly not indicated at all strongly as judged by the "regression" line of means, except possibly in the case of benzene. Certain abnormally low leucocyte counts, as we would judge them to be from the generally accepted standards, would both in the case of toluene and benzene point to a blood lesion. A correlation between length of exposure to the poisonous effect of these substances may not be easy to demonstrate, if the effects are entirely contrary at different periods or with different concentrations. A leucocytosis due to a stimulating effect in early stages of action or in low concentrations might easily mask the leucopenia of later stages and of higher concentrations. There is also another factor which may be selectively operative in the populations affected and that is one of elimination of the unduly sensitive. Those who have an idiosyncrasy or a special sensitiveness leave their occupations and are not to be found among the workers examined. An inspection of the tables shows that the criteria laid down by the American Committee on Benzol would have necessitated the withdrawal of workers both with toluene and with benzene from their employment because they had passed the danger point.

IV. EXPERIMENTS ON ANIMALS.

The animals on which we tested the effects of benzene and toluene were rabbits and white rats, and the methods used were subcutaneous injection and inhalation. As so much depends in a research of this type, where a number of animals is concerned and day to day observations are being made, on a knowledge of the variation which may normally occur in the animal species used, we consider it essential to set out the data available for normal animals. It has not been possible for us to set up frequency distributions of our own for these animals as our observations are too few in number, but the animal's blood was always examined once before any test was begun. The best data to our knowledge, as regards rabbits, are those of Pearce and Casey (1930) and are given in biometric form, with frequencies as percentages of occurrence. The relative graphs are reproduced in Figs. I–IV.

In Table I of the same authors the abbreviated and mean results are given of 1110 blood counts on 174 rabbits, as set out in Table VIII:

Table VIII.

	Mean	Minimum	Maximum	Standard Deviation
Erythrocytes	5,198,000 ± 12,700	3,020,000	8,040,000	628,250
Haemoglobin (%)	63 ± 2	28	90	10
Leucocytes	9,562 ± 59	3,150	23,500	2,919
Neutrophils	4,341 ± 37	1,050	15,390	1,823
Basophils	950 ± 13	0	5,359	635
Eosinophils	214 ± 4	0	1,760	217
Lymphocytes	3,045 ± 28	630	9,900	1,366
Monocytes	1,000 ± 12	72	5,405	571

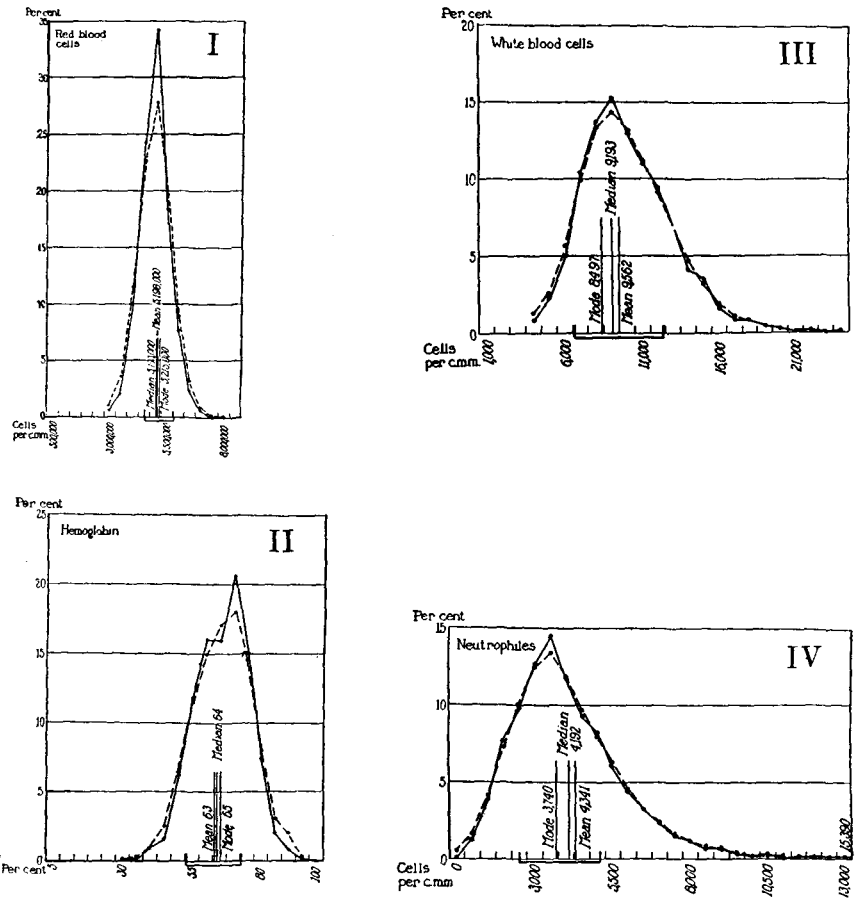

Fig. I. Percentage frequency distribution of erythrocytes per c.mm., in rabbits.
Fig. II. Percentage frequency distribution of haemoglobin content, in rabbits.
Fig. III. Percentage frequency distribution of total leucocytes per c.mm., in rabbits.
Fig. IV. Percentage frequency distribution of total neutrophils (polymorphonuclears) per c.mm., in rabbits.

We may take as our figures for rats the published data of Klieneberger and Carl (1912) to some extent modified by us (transitionals taken as monocytes), as set out in Table IX.

All our animals were examined between 10 and 11 a.m. and had already been fed. A factor which may require attention is the effect of the trauma of blood sampling. In our inhalation experiments on rats the animal was confined in a tall roomy bell-jar with inlet for vapour at the bottom and outlet at the top. A water pump served to draw air through benzene or toluene as the case may be, and the amount by which the fluid in each case was diminished at the end of the experiment was taken as the index of the relative concentration of the vapour in each case. Both the benzene and the toluene used were obtained

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Table IX.

Erythrocytes	Leucocytes	Neutrophils %	Lymphocytes %	Monocytes %	Eosinophils %
A. *Ordinary feeding.* (Blood from femoral vessels.)					
1. 9,060,000	13,900	14	82	1	3
2. 9,925,000	10,800	12·5	83	2·75	1·75
3. 9,230,000	18,800	8·75	87·5	1·75	2
4. 9,340,000	12,300	12	81·5	3·5	3
5. 9,525,000	16,150	11	82	2	5
6. 9,140,000	16,250	25	64·5	3	7·5
7. 9,308,000	13,350	17·5	76·25	3·75	2·5
8. 8,308,000	20,500	16·25	78·5	1·5	3·75
B. *Fasting.* (Tail blood.)					
9. —	25,050	11	88·5	0·5	4
10. —	21,300	20·5	74	0	5·5
11. —	19,500	17·5	77·5	2	3
12. —	18,000	17	75	1	7
C. *After food.* Sättigung. (Tail blood.)					
13. —	42,000	39·33	59·83	0·5	0·33
14. —	22,700	19·5	78·2	0	2·33
15. —	27,450	59·66	38·33	0·33	1·66
16. —	8,725	44·66	53·66	0	1·66

from our chemical department and were labelled "pure." For equal times of use of the exhaust pump the amount of benzene carried over was about twice that of toluene, which is in accordance with the relative volatilities of the two substances. In our later comparative experiments we doubled the time of exposure of animals to toluene in order to counteract to some extent this inequality. It is scarcely possible to regard these inhalation experiments as illustrative of chronic poisoning, however, for the effect was acute and the exposure had to be short in order to avoid the death of the animal. These were, therefore, a succession of daily acute poisonings, either once or twice a day, to the stage of narcosis, each of which was rapidly recovered from. It may be that we have in this fact part of the explanation that the blood picture which followed could scarcely be called—at least in the majority of cases—a neutropenia or even an agranulocytic anaemia. The symptoms produced by inhalation for both benzene and toluene—and we could make out little difference between them—were excitation, facial irritation perhaps of ocular and nasal surfaces, incoordination of muscular movement with want of balance, narcosis of an imperfect type accompanied by twitching and rapid recovery with removal from the testing chamber. Our subcutaneous injection experiments conformed more or less in technique (mixture of reagent with olive oil in equal quantities) to those originally devised by Selling, which have been practically adopted by everyone. It is not possible to set out all the figures and charts relating to our tests, although we should like to do so in order to show the variability or, as the case may be, absence of effect obtained with both of the test substances. We present here then the results obtained in two rabbits

(see Fig. VI, p. 564), one injected subcutaneously with benzene and one with toluene, and in two rats (see Fig. V), illustrating inhalation experiments with the same two substances. The charts here given show the day-to-day position of the animals as regards total erythrocytes, total leucocytes, and reticulocyte percentages. In Tables X–XIII, which cover the same period, we give the differential total and percentage counts for the different types of leucocyte and the weights of the animals as the experiment progressed.

Table X. *Showing the effect of inhalation of benzene* (*Rat* 106) *twice daily* (*Sundays excepted*) *on the peripheral blood picture.*

	Days after commencement of inhalations					
	0	**1**	**2**	**3**	**4**	**5**
Neutrophils	1,106 (29·5 %)	1,853 (19 %)	4,471 (24·5 %)	5,400 (24 %)	1,853 (19·5 %)	5,018 (22·3 %)
Lymphocytes	2,475 (66)	6,435 (66)	12,501 (68·5)	15,908 (70·7)	7,125 (75)	14,715 (65·4)
Monocytes	169 (4·5)	1,462 (15)	1,095 (6)	1,192 (5·3)	475 (5)	2,340 (10·4)
Eosinophils	0	0	183 (1)	0	47 (0·5)	427 (1·9)
Exposure (min.)	4	4	4	4	4	4
Benzene (c.c.)*	5·5	6·6	6·7	7	8·1	7·6
Weight (g.)	144	142	148	150	142	156

* These amounts represent the total quantity which had passed over in the two exposures of the day.

	Days after commencement of inhalations					
	7	**8**	**9**	**10**	**11**	**12**
Neutrophils	3,444 (14·5)	2,500 (20)	3,025 (22)	2,745 (24·5)	3,106 (27)	5,250 (30)
Lymphocytes	17,100 (72)	9,000 (72)	8,181 (59·5)	6,817 (60·6)	7,877 (68·5)	10,062 (37·5)
Monocytes	3,088 (13)	500 (4)	2,406 (17·5)	1,474 (13·1)	402 (3·5)	2,100 (12)
Eosinophils	118 (0·5)	500 (4)	138 (1)	214 (1·9)	115 (1)	87 (0·5)
Exposure (min.)	4	4	4	6	6	6
Benzene (c.c.)	8·8	8·8	9	11·5	9·3	6·6
Weight (g.)	150	154	156	162	160	157

	Days after commencement of inhalations					
	14	**15**	**16**	**17**	**18**	**19**
Neutrophils	3,320 (23·3)	2,760 (23)	4,144 (25·9)	2,734 (24·3)	1,957 (18·2)	4,254 (20·5)
Lymphocytes	7,823 (54·9)	7,596 (63·3)	10,544 (65·9)	6,773 (60·2)	6,772 (63)	13,902 (67)
Monocytes	2,836 (19·9)	1,296 (10·8)	1,232 (7·7)	1,642 (14·6)	1,817 (16·9)	2,179 (10·5)
Eosinophils	271 (1·9)	348 (2·9)	80 (0·5)	101 (0·9)	204 (1·9)	415 (2)
Exposure (min.)	6	6	6	6	6	6
Benzene (c.c.)	10	9·5	9	9·6	7·6	8·5
Weight (g.)	156	149	144	142	144	148

	Days after commencement of inhalations					
	21	**22**	**23**	**24**	**25**	**26**
Neutrophils	3,535 (20·2)	2,552 (31·9)	3,316 (26·8)	6,217 (30·7)	4,216 (24·8)	4,465 (44·1)
Lymphocytes	12,793 (73·1)	4,472 (55·9)	8,242 (66·6)	11,502 (56·8)	11,220 (66)	4,546 (44·9)
Monocytes	1,015 (5·8)	976 (12·2)	817 (6·6)	2,531 (12·5)	1,513 (8·9)	1,023 (10·1)
Eosinophils	157 (0·9)	0	0	0	51 (0·3)	91 (0·9)
Exposure (min.)	6	6	6	6	6	6
Benzene (c.c.)	8·6	10·6	10·5	7·5	9·2	10·7
Weight (g.)	138	150	152	153	157	156

	Days after commencement of inhalations				
	28	**29**	**30**	**31**	**32**
Neutrophils	3,892 (30·7)	3,669 (25·3)	2,315 (19·5)	2,105 (14·9)	2,242 (13·9)
Lymphocytes	7,263 (57·3)	7,786 (53·7)	8,301 (69·9)	9,718 (68·8)	10,304 (63·9)
Monocytes	1,483 (11·7)	2,871 (19·8)	1,259 (10·6)	2,246 (15·9)	3,176 (19·7)
Eosinophils	37 (0·3)	174 (1·2)	0	56 (0·4)	403 (2·5)
Exposure (min.)	6	6	8	8	4
Benzene (c.c.)	5·8	11	12·2	12	8
Weight (g.)	160	157	155	153	152

Table XI. *Showing the effect of inhalation of toluene* (*Rat* 104) *twice daily for two minutes* (*Sundays excepted*) *on the peripheral blood picture.*

	Days after commencement of inhalations				
	0	**1**	**2**	**3**	**4**
Neutrophils	1,425 (28·5)	3,740 (34)	3,510 (39)	2,465 (29)	4,136 (37·6)
Lymphocytes	3,400 (68)	6,765 (61·5)	4,725 (52·5)	4,803 (56·5)	6,369 (57·9)
Monocytes	150 (3)	495 (4·5)	585 (6·5)	1,062 (12·5)	495 (4·5)
Eosinophils	25	0	180	170	0
Exposure (min.)	8	8	8	8	8
Toluene (c.c.)*	3·5	3·2	3·2	3·5	4·2
Weight (g.)	160	154	154	150	154

* These amounts represent the total quantity which had passed over in the two exposures of the day.

	Days after commencement of inhalations				
	5	**7**	**8**	**9**	**10**
Neutrophils	3,675 (35)	3,255 (31)	2,423 (25·5)	2,200 (22)	2,520 (24)
Lymphocytes	6,510 (62)	6,510 (62)	6,697 (70·5)	7,250 (72·5)	7,718 (73·5)
Monocytes	313 (3)	578 (5·5)	380 (4)	350 (3·5)	262 (2·5)
Eosinophils	0	157	0	200 (2)	0
Exposure (min.)	8	8	8	8	8
Toluene (c.c.)	3	5·8	6·8	4·3	5·4
Weight (g.)	150	148	164	170	172

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	Days after commencement of inhalations				
	11	**12**	**14**	**15**	**16**
Neutrophils	2,500 (25)	2,306 (22·5)	1,388 (15)	563 (7·5)	1,434 (15·5)
Lymphocytes	7,250 (72·5)	7,533 (73·5)	7,215 (78)	6,638 (88·5)	7,261 (78·5)
Monocytes	150 (1·5)	410 (4)	601 (6·5)	262 (3·5)	463 (5)
Eosinophils	100 (1)	0	46 (0·5)	37 (0·5)	92 (1)
Exposure (min.)	8	8	8	8	8
Toluene (c.c.)	6	6	7·6	6	6·3
Weight (g.)	160	174	172	168	174

	Days after commencement of inhalations				
	17	**18**	**19**	**21**	**22**
Neutrophils	1,601 (10·5)	1,163 (15·5)	2,351 (16·5)	1,590 (12)	2,828 (19·5)
Lymphocytes	11,743 (77)	5,475 (73)	10,688 (75)	9,805 (74)	10,295 (71)
Monocytes	1,830 (12)	787 (10·5)	1,069 (7·5)	1,855 (14)	1,087 (7·5)
Eosinophils	76 (0·5)	75 (1)	142 (1)	0	290 (2)
Exposure (min.)	10	10	10	10	0
Toluene (c.c.)	11·9	8·7	9·6	8·3	0
Weight (g.)	174	174	177	175	168

Table XII. *Showing the effect of subcutaneous injection of benzene daily (1 c.c. per kg.) on the peripheral blood picture. Rabbit* 107.

	Days after commencement of injections					
	0	**1**	**2**	**3**	**4**	**5**
Neutrophils	2,520 (35·5)	6,419 (65·5)	3,626 (37)	3,240 (43·2)	4,017 (51·5)	2,531 (42·9)
Lymphocytes	4,189 (59)	3,185 (32·5)	5,782 (59)	3,720 (49·6)	3,455 (44·3)	3,151 (53·4)
Monocytes	178 (2·5)	49 (0·5)	245 (2·5)	480 (6·4)	265 (3·4)	159 (2·7)
Eosinophils	36 (0·5)	49 (0·5)	0	30 (0·4)	0	59 (1)
Basophils	177 (2·5)	98 (1)	147 (1·5)	30 (0·4)	63 (10·8)	0
% Nucleated erythrocytes	0	0	0	6·41	9·79	1·7
Weight (g.)	2,876	2,815	2,761	2,776	2,943	2,854

	Days after commencement of injections					
	7	**8**	**9**	**10**	**11**	**12**
Neutrophils	1,280 (41·3)	873 (29·6)	673 (17·7)	2,659 (27·7)	5,673 (46·5)	3,616 (70·9)
Lymphocytes	1,779 (57·4)	1,982 (57·2)	3,066 (80·7)	6,394 (66·6)	6,051 (49·6)	1,260 (24·7)
Monocytes	16 (0·5)	68 (2·3)	61 (1·6)	480 (5)	402 (3·3)	209 (4·1)
Eosinophils	25 (0·8)	18 (0·6)	0	48 (0·5)	37 (0·3)	0
Basophils	0	9 (0·3)	0	19 (0·2)	37 (0·3)	15 (0·3)
% Nucleated erythrocytes	1·7	1·6	6·6	3·5	3·6	2·2
Weight (g.)	2,869	2,841	2,881	2,863	2,794	2,815

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	Days after commencement of injections				
	14	**15**	**16**	**17**	**18**
Neutrophils	801 (43·3)	321 (21·4)	297 (15·6)	588 (28·7)	796 (32·5)
Lymphocytes	1,012 (54·7)	1,167 (77·8)	1,150 (81·6)	1,424 (69·5)	1,622 (66·2)
Monocytes	37 (2)	12 (0·8)	53 (2·8)	26 (1·3)	31 (1·3)
Eosinophils	0	0	0	0	0
Basophils	0	0	0	12 (0·6)	0
% Nucleated erythrocytes	0·9	0·6	4·5	2·7	4
Weight (g.)	2,839	2,836	2,844	2,809	2,680

Table XIII. *Showing the effect of subcutaneous injection of toluene daily (1 c.c. per kg.) on the peripheral blood picture. Rabbit* 110.

	Days after commencement of injections					
	0	**1**	**2**	**4**	**5**	**6**
Neutrophils	4,506 (35·2)	2,945 (39·8)	3,071 (28·3)	1,929 (21·8)	3,780 (31·5)	2,608 (20·7)
Lymphocytes	7,744 (60·5)	3,893 (52·6)	7,183 (66·2)	6,160 (69·6)	6,780 (56·5)	8,329 (66·1)
Monocytes	64 (0·5)	118 (1·6)	130 (1·2)	106 (1·2)	528 (4·4)	718 (5·7)
Eosinophils	0	52 (0·7)	0	106 (1·2)	216 (1·8)	302 (2·4)
Basophils	486 (3·8)	392 (5·3)	466 (4·3)	549 (6·2)	696 (5·8)	643 (5·1)
% Nucleated erythrocytes	0	0	0	0	0	0·49
Weight (g.)	2,250	2,060	2,073	2,053	2,080	2,036

	Days after commencement of injections					
	7	**8**	**9**	**11**	**12**	**13**
Neutrophils	2,267 (15·8)	2,502 (15·8)	2,280 (28·5)	2,933 (27·8)	6,236 (41·3)	4,933 (34·5)
Lymphocytes	9,687 (67·5)	7,050 (66·5)	5,000 (62·5)	6,910 (65·5)	7,667 (52·1)	8,294 (58)
Monocytes	904 (6·3)	381 (3·6)	104 (1·3)	243 (2·3)	317 (2·1)	415 (2·9)
Eosinophils	817 (5·7)	222 (2·1)	248 (3·1)	105 (1)	287 (1·9)	315 (2·2)
Basophils	675 (4·7)	445 (4·2)	368 (4·6)	359 (3·4)	393 (2·6)	343 (2·4)
% Nucleated erythrocytes	0	0	0	0·2	0	0
Weight (g.)	2,080	2,046	2,014	2,066	2,041	2,038

	Days after commencement of injections					
	14	**15**	**16**	**18**	**19**	**20**
Neutrophils	3,745 (33·9)	2,712 (28·4)	2,279 (21·1)	3,748 (26·3)	4,150 (40·1)	2,769 (28·7)
Lymphocytes	6,508 (59·8)	6,274 (65·7)	8,003 (74·1)	9,448 (66·3)	5,558 (53·7)	6,292 (65·2)
Monocytes	221 (2)	153 (1·6)	151 (1·4)	185 (1·3)	290 (2·8)	318 (3·3)
Eosinophils	144 (1·3)	133 (1·4)	65 (0·6)	185 (1·3)	41 (0·4)	39 (0·4)
Basophils	331 (3)	276 (2·9)	302 (2·8)	684 (4·8)	311 (3)	232 (2·4)
% Nucleated erythrocytes	0	0	0	0	0	0·21
Weight (g.)	2,051	1,990	1,990	1,943	1,984	2,065

	Days after commencement of injections					
	21	**22**	**23**	**25**	**26**	**27**
Neutrophils	5,308 (44·6)	5,207 (39·9)	2,576 (27·7)	3,943 (38·1)	3,602 (40·7)	2,779 (28·8)
Lymphocytes	5,783 (48·6)	7,186 (54·3)	6,194 (66·6)	5,837 (56·4)	4,505 (50·9)	6,176 (64)
Monocytes	238 (2)	183 (1·4)	149 (1·6)	52 (0·5)	142 (1·6)	125 (1·3)
Eosinophils	131 (1·1)	65 (0·5)	37 (0·4)	104 (1)	150 (1·7)	77 (0·8)
Basophils	440 (3·7)	509 (3·9)	544 (3·7)	414 (4)	451 (5·1)	493 (5·1)
% Nucleated erythrocytes	0·18	0	2·4	0·4	0·23	3·06
Weight (g.)	2,065	2,065	2,080	2,045	2,070	2,160

	Days after commencement of injections					
	28	**29**	**30**	**32**	**33**	**34**
Neutrophils	3,818 (42·9)	3,534 (33·5)	4,242 (35·8)	4,149 (43)	5,136 (46·9)	5,545 (54·1)
Lymphocytes	4,441 (49·9)	5,877 (55·7)	6,707 (56·6)	4,912 (50·9)	4,927 (45)	4,244 (41·4)
Monocytes	170 (1·9)	306 (2·9)	190 (1·6)	58 (0·6)	77 (0·7)	102 (1)
Eosinophils	124 (1·4)	274 (2·6)	119 (1)	106 (1·1)	241 (2·2)	154 (1·5)
Basophils	347 (3·9)	559 (5·3)	592 (5)	425 (4·4)	569 (5·2)	205 (2)
% Nucleated erythrocytes	1·19	0·39	0·61	0	0	0·21
Weight (g.)	2,160	2,167	2,180	2,084	2,160	2,250

	Days after commencement of injections			
	35	**36**	**37**	**39**
Neutrophils	2,175 (33·2)	3,791 (39·9)	4,705 (38·1)	5,765 (42·7)
Lymphocytes	3,589 (54·8)	5,025 (52·9)	6,595 (53·4)	6,466 (47·9)
Monocytes	354 (5·4)	219 (2·3)	222 (1·8)	54 (0·4)
Eosinophils	98 (1·5)	114 (1·2)	210 (1·7)	351 (2·6)
Basophils	334 (5·1)	351 (3·7)	618 (5)	864 (6·4)
% Nucleated erythrocytes	0	0	0	0
Weight (g.)	2,210	2,190	2,210	2,040

Autopsies.

These were done on all the test animals and may be said to have presented more or less similar appearances in all of them. In general the effect on the bone marrow was one of stimulation of activity and production of a decidedly red cellular marrow; on the spleen of congestion, little or no haemosiderosis, prominence of reticulum cells in contrast to lymphocytes, but no myeloid metaplasia; on the liver of no very marked effect and on the lung of congestion

and haemorrhage but no fat embolism. We may very briefly indicate the findings from our notes on Rabbits 107 (benzene) and 110 (toluene).

Rabbit 107. *Benzene. Killed by chloroform.*

No signs of sepsis were seen at the sites of inoculation and no subcutaneous haemorrhages. The peritoneal cavity was noticeably very full of fat, omental, subperitoneal, perivascular and perinephric. Nothing was to be noted with

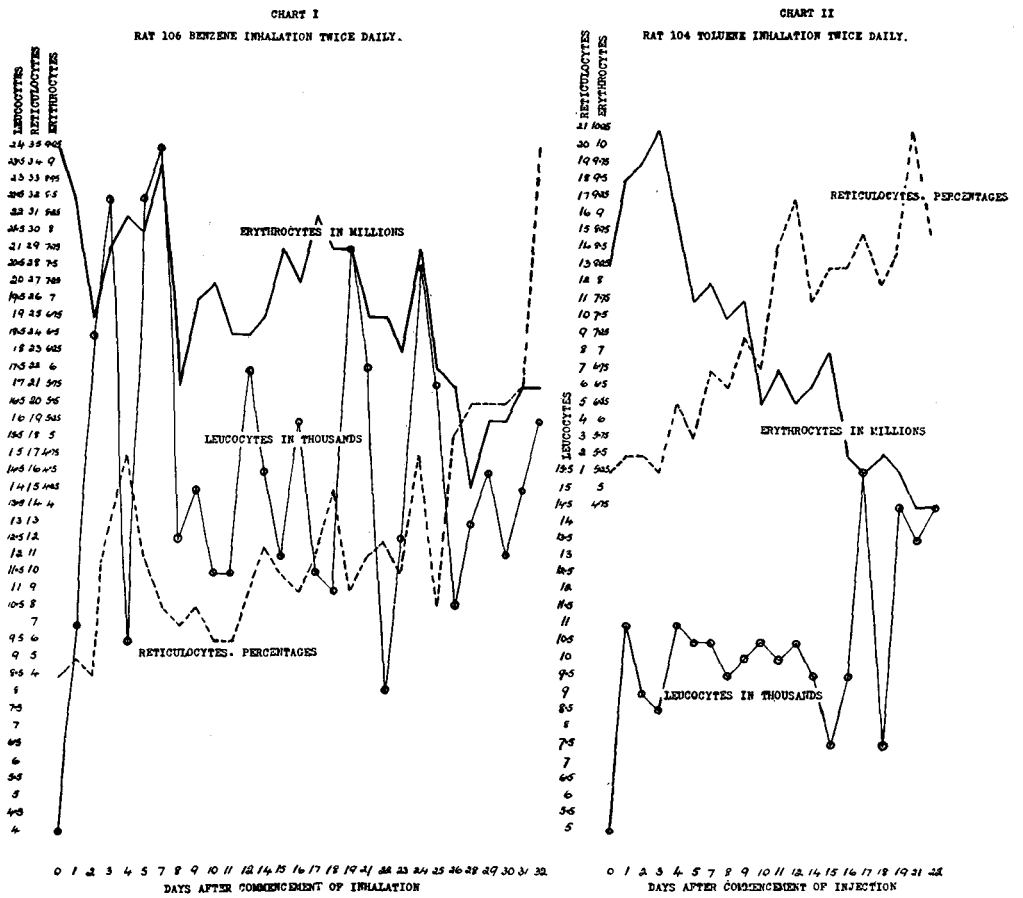

Fig. V. (Charts I and II.) Showing the effect of inhalations of benzene (rat 106) and toluene (rat 104) twice daily (Sundays excepted) on the peripheral blood picture.

regard to heart, lungs, intestine, kidneys, suprarenals, spleen, brain and spinal cord. No subperitoneal and no subpleural haemorrhages were present. The stomach was full of food. Bone marrow was red and redundant throughout the shaft of the femur. All the tissues were fixed immediately on removal in warm Zenker's fluid. Microscopical examination showed:

Spleen. The general appearance was of a spleen with greatly thickened capsule, thickened trabeculae and well demarcated pulp cords. The endo-

thelium of the sinuses stood out prominently and served to characterise them as anastomosing channels. Along with the erythrocytes in the sinuses there were numerous large cells with vesicular lightly chromatic nucleus which are presumably reticular cells. They did not show especially phagocytic characters either of erythrocytes or haemosiderin. There were no polymorph leucocytes in the sinuses, but there were a few lymphocytic cells. In the pulp cords the

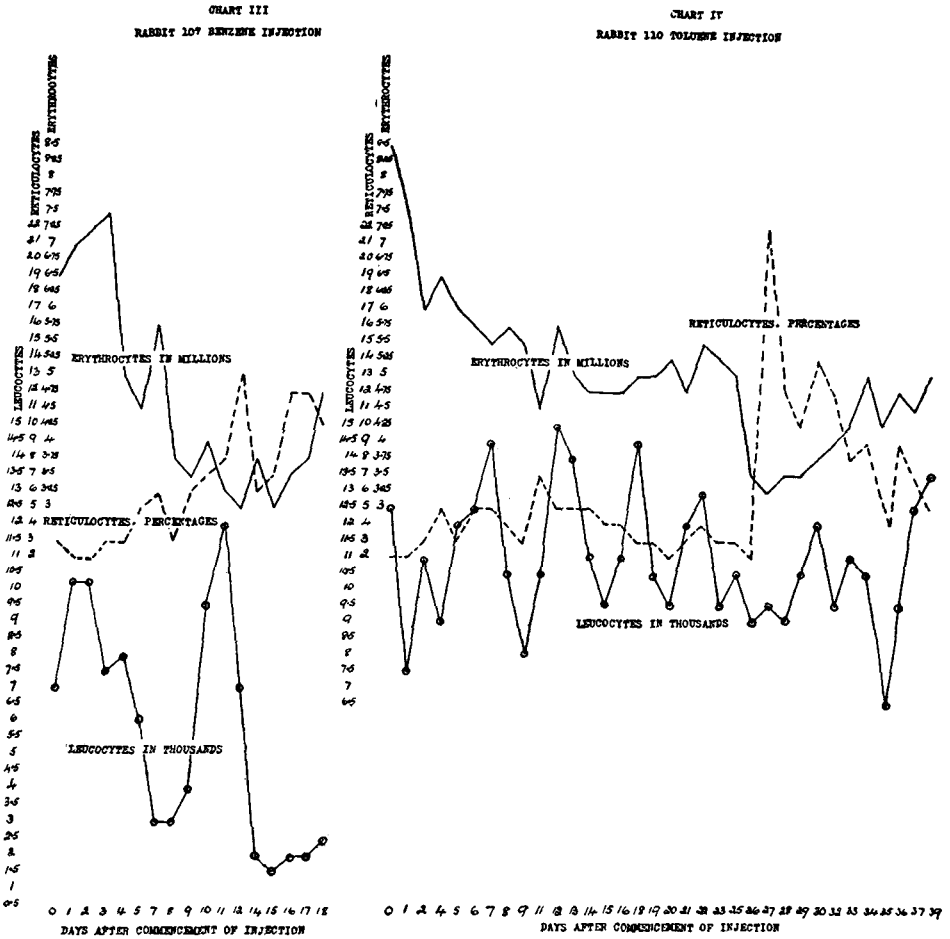

Fig. VI. (Charts III and IV.) Showing the effect of injections of benzene (rabbit 107) and toluene (rabbit 110) daily (1 c.c. per kg.) on the peripheral blood picture.

component cell was of the elongated type of reticular cell. Malpighian bodies were distinct, usually with several enclosed thickened arterioles, mainly composed of small lymphocytes and without sign of a germinal centre. The Malpighian bodies proper passed by gradation into reticular cells which formed their periphery. No indication of myeloid metaplasia and no Prussian blue reaction were found.

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Liver. The liver cells were swollen and highly granular and the sinusoids were compressed by the swollen parenchyma. No haemosiderosis was observable.

Kidney. The glomeruli were prominent with abundant nuclei. No exudate was to be seen in Bowman's capsule. Granularity was apparent in the epithelium of the tubules. No very evident pathological condition could be made out.

Lung. There was congestion of alveolar vessels. No infarction, no haemorrhage and no pneumonia were to be made out.

Bone marrow (femur shaft). The stains used were haematoxylin-eosin and eosin-methylene blue. A cellular parenchymatous bone marrow with discrete fat cells was the general appearance. The sinuses were full of erythrocytes and were well defined by their lining endothelium. In the parenchyma the myeloid elements appeared to be well represented—myeloblasts, large numbers of neutrophile and eosinophile myelocytes, metamyelocytes, but rather few polymorphs; none of these showed signs of degeneration—rather a general myeloid hyperplasia with abundance of the primitive type cells. Mitoses were fairly abundant. There were numerous normoblast erythrocytes present and, presumably, corresponding erythroblasts. The megakaryocytes were in large number, sometimes in islands and well formed. No iron reaction was obtained with Prussian blue.

Rabbit 110. *Toluene. Killed by chloroform.*

No signs of sepsis were seen at the sites of inoculation and no subcutaneous haemorrhages. No emaciation existed, but there was no superabundance of fat. Nothing was to be noted with regard to heart, intestine, kidneys, suprarenals, spleen, brain and spinal cord. No subperitoneal haemorrhages were present. The left lung was distinctly mottled with yellowish areas and the right lung was similar to the left but not quite so markedly mottled: dark haemorrhagic-looking areas were seen at the apex. The bone marrow was red and abundant throughout the shaft of the femur. Microscopical examination showed:

Spleen. The general appearance rather suggested a diffusion of Malpighian body tissue with extension along the course of the arterioles. The capsule and trabeculae not only were not thickened, but appeared to be distended. The sinuses stood out prominently with well-defined endothelium, were distended with erythrocytes and contained very numerous large reticular cells and also numerous polymorphs. It was noticeable that the nuclei of the polymorphs were in some cases undergoing fragmentation. No phagocytosis of erythrocytes and only slight haemosiderosis were evident. In the pulp cords the reticular cells were large, prominent and abundant, to the extent of forming the majority of the cells present. In the Malpighian bodies the large reticular cells similar to those of the pulp cords passed well into the centre. In the centre itself the lymphocytic element was predominant. No well-marked germinal centres were seen, but mitoses were fairly numerous. No indication of myeloid

metaplasia was apparent. A Prussian blue reaction was evident in a few phagocytic cells only. Eosinophile cells were fairly abundant in both cords and sinuses.

By comparison the spleen in rabbit 107 had more thickened capsule, trabeculae and Malpighian arterioles, its sinuses were less dilated with blood, it had much fewer of the large reticular cells and very much fewer polymorph leucocytes than that of rabbit 110.

Liver. Its cells were coarsely granular but not unduly swollen. The sinuses contained a considerable amount of blood.

Kidney. Glomeruli were prominent with abundant nuclei. Blood and lymph were present in Bowman's capsule. Blood and coarse granular debris were seen in both secreting and collecting tubules.

Lung. Congestion of alveolar vessels was well marked. A prominent feature was the great eosinophile polymorphonuclear infiltration especially at the pleural surface and around blood vessels. The extreme apical portion was almost solid with hypertrophy of alveolar epithelium and numerous eosinophils and the alveoli were obliterated. The eosinophils throughout this lung were very striking. Some small haemorrhages were present just below the pleural surface and it is probably these which gave rise to the mottling. Haemorrhage had also occurred into some of the bronchi.

Bone marrow (femur, shaft). A cellular parenchymatous bone marrow with discrete fat cells was the general appearance: it was a more cellular marrow than in rabbit 107. The sinuses also were not so distended with erythrocytes as in rabbit 107. In the parenchyma all the myeloid elements appeared to be well represented with a distinct predominance of neutrophile polymorphonuclears. Neutrophile and a fair number of eosinophile, myelocytes and metamyelocytes were well represented—in fact a polymorphonuclear type of reaction with an abundance of eosinophile myelocytes was the impression given by the section. Normoblasts were abundant. There were a fair number of mitoses. The megakaryocytes were numerous. Some of their nuclei appeared distinctly abnormal, hyperchromatic and pycnotic and showed some karyorrhexis. No Prussian blue reaction could be obtained.

Discussion of experiments on animals.

A discussion based on the results obtained with four animals only would not have great validity. Indeed it is evident to anyone who studies this question of the action of benzene and its homologues that a great deal more work still requires to be done if only to reconcile the great diversity of opinion and findings on the subject. Our experimentation, however, is not confined to four animals but extends to a considerable number, more precisely eight rabbits and eleven rats. It is the sum total of experiments which we take into account then, as well as those specially chosen, because they were uncomplicated and illustrative. We judge from these that benzene is rather more toxic than toluene although this has to be qualified by the fact that the dosage is unequal

in the two cases, being greater for benzene than for toluene. Our experiments have not furnished results altogether similar to those of others. The benzene which we used on the strains of rabbits and rats employed did not provide the spectacle of a well-marked neutropenia with less effect on the erythrocyte system. In fact the effect was almost a reversal of this, in that anaemia was even more marked than leucopenia and that an erythropoietic disturbance was rather more manifest in the peripheral blood picture than a leucopoietic (see Figs. 5 and 6). The reticulocyte curves run very similarly, although with opposite direction to the erythrocyte curves (see Figs. 5 and 6). A study of the counts of nucleated red cells seems to show that these made their appearance very irregularly in what we may call "showers"—to use an appellation which haematologists have made current. The curves indicate that, as has also been suggested by other workers, the reticulocyte percentage count, so easy to apply, might be more frequently used than it is, as an indicator of the state of bone marrow or haemopoietic activity. As regards the important question with which we have more or less set out to deal, that of the relative toxicities of benzene and toluene, we conclude from these animal experiments, as we have already said, that benzene being more volatile is more toxic than toluene, but that both of these substances have similar symptomatic effects on animals, a very definite action on the blood-forming organs and perhaps a destructive effect on the circulatory blood cells themselves. We have not obtained that rapid leucopenia in a few days after injection or inhalation which other workers have found. All our examinations of the peripheral blood were made in the morning before any subjection of the animal to the effect of injection or inhalation. We may wonder indeed whether some of the leucopenic effects described are not those non-specific blood effects of which Harvey and Hamilton (1932) have treated. Our opinion indeed is crystallising in the direction that the action of benzene or its homologues is not as singular in incidence upon the blood cells as it is generally made out to be and that its effect is a varied one, not necessarily neutropenia, anaemia nor thrombopenia, a stimulant as much as a destroying agent, and generally speaking more or less non-specific. The further discussion of this subject is held over till later on.

V. EXAMINATION OF WORKERS USING BENZENE OR BENZENE HOMOLOGUES.

An examination was made of ten employees whose work exposed them to the vapour of an industrial solvent containing approximately 45 per cent. toluene, but no benzene (about 60 per cent. of the solvent used is reclaimed by a recovery plant). These men were compared with a similar number belonging to the same factory who were not subject to this risk, and again with a similar number of individuals working in our own laboratory. All were adult males of varying age. A questionary of possible symptoms was put to the factory employees and they were also examined for anaemia, pharyngitis, tremor, state of the knee jerks and goitre. In fact one might say that there were no

specific complaints. The blood picture in these cases is perhaps more instructive than other signs and symptoms, for it was not in any way affected by apprehension regarding the meaning of our enquiry. We give this *in extenso* (see Table XIV) for the classes of persons examined, as it has an interest for the wider question of general variation of blood data within normal limits.

Table XIV.

1. *Employees exposed to risk from solvent.*

											Means
Erythrocytes	4·976	5·136	6·336	5·584	5·024	5·92	6·496	4·816	4·096	5·376	5·4
Leucocytes	7·825	8·025	13·925	8·85	6·45	5·25	13·2	7·35	4·75	6·825	8·2
Neutrophils	60·3	57·3	72·0	56·1	47·4	48·8	50·7	70·7	53·9	47·5	
Lymphocytes	34·9	28·5	24·7	37·5	42·2	44·0	45·7	26·2	42·3	42·3	
Monocytes	3·6	8·5	2·7	4·5	9·5	4·3	2·8	2·5	2·6	4·9	
Eosinophils	1·2	4·7	0·4	1·5	0·7	2·0	0·8	0·2	1·2	4·9	
Basophils	0	1·0	0·2	0·4	0·2	0·9	0	0·4	0	0·4	

2. *Employees not exposed to risk from solvent.*

											Means
Erythrocytes	6·08	6·064	5·472	4·032	6·128	5·904	5·616	4·56	4·448	6·256	5·5
Leucocytes	7·4	8·45	9·75	9·7	4·975	10·9	6·95	9·825	5·75	10·35	8·4
Neutrophils	61·0	44·5	48·7	74·3	61·9	59·3	47·6	54·8	49·2	48·4	
Lymphocytes	31·6	48·0	45·0	20·8	29·7	33·8	38·8	38·4	42·1	40·2	
Monocytes	4·0	5·8	5·0	4·1	5·9	4·5	6·7	4·8	4·5	5·5	
Eosinophils	1·5	1·0	1·3	0·8	0·9	2·0	6·1	1·1	4·1	4·5	
Basophils	0·9	0·7	0·5	0	1·6	0·4	0·8	0·9	0·1	1·4	

3. *Laboratory Workers.*

											Means
Erythrocytes	4·976	5·216	5·392	5·328	5·088	5·536	5·36	5·808	5·664	5·168	5·4
Leucocytes	6·925	9·975	7·125	7·425	6·3	9·95	9·525	9·1	6·35	6·25	7·9
Neutrophils	66·8	59·3	53·6	51·9	54·9	62·0	68·4	59·3	62·2	49·7	
Lymphocytes	23·9	29·6	37·2	39·0	37·8	31·9	27·3	35·0	33·8	37·3	
Monocytes	5·9	6·1	7·6	2·0	4·0	5·2	1·6	3·2	2·7	11·4	
Eosinophils	1·5	4·3	1·2	5·9	3·1	0·9	2·3	1·0	1·1	1·3	
Basophils	1·9	0·7	0·4	1·2	0·2	0	0·4	1·5	0·2	0·3	

The differences between these three small groups are, as far as one can see, insignificant.

The types of leucocytes are given in percentages. The figures for total erythrocytes and total leucocytes are for millions and thousands respectively. No nucleated erythrocytes, polychromasia or increase of reticulocyte percentage were noticed in any individual.

VI. Clinical and pathological description of a case of anaemia in a toluene worker.

F.M., a stockily-built, athletic subject, 38 years of age, had been in charge of the solvent recovery apparatus over the spreading tables at an india-rubber factory since 1919. The solvent handled contained about 45 per cent. toluene, but no benzene, and his work brought him into intimate contact with it: mean workroom temperatures, summer D.B. 88° R.H. 60; winter D.B. 79° R.H. 62. His health had been good prior to 1930, when he had the misfortune to receive a severe blow on the face while playing hockey. His nose was broken, and since that time he had been subject to nose-bleeding and headaches. He returned to work a few weeks after the accident, and, apart from the headaches, felt reasonably well till March, 1932, when haemorrhagic spots

began to appear on his tongue. About this time he was rejected by a Life Assurance Company after examination of his urine, which was then described as "smoky." Successive crops of spots continued to appear on his tongue, and on the buccal mucous membrane (see Fig. VII). He had a severe nose-bleeding,

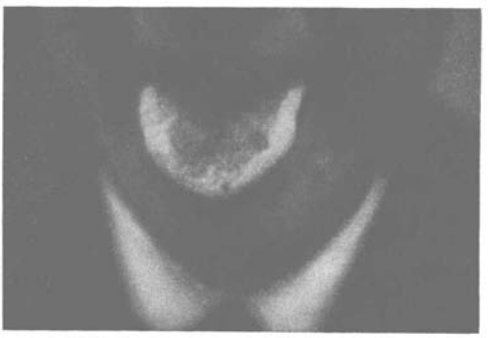


Fig. VII. See explanation in text.

lasting one day and one night, on 19th June, and a week later his lower gums commenced to bleed. This bleeding continued intermittently, and each fresh bleeding was heralded by bilateral pains in front of the angle of the jaw and followed by severe headache. He complained of eye pains and of "neuritis" involving particularly his left leg; but not of digestive disturbance. His general condition continued to deteriorate, and about the middle of August he was referred to Dr Goodall's O.P. Clinic at Edinburgh Royal Infirmary. A blood count was then made with the following result:

Red blood cells	...	4,000,000
Hb	...	75 per cent.
White blood cells	...	2,200

Coagulation time, markedly delayed.

By the end of September he showed definite pallor of the skin and mucous membranes: bleedings from gums and into membranes continued. He had on the left cheek a fluctuating swelling, while marks of subcutaneous haemorrhages were to be seen on his hands and face. There was no enlargement of liver or spleen. The results of repeated blood examinations are summarised in Table XV.

In view of the continued fall of the leucocyte count he was admitted to hospital on October 27th. Shortly after admission his temperature rose to 103° F., with symptoms of a severe cold. Examination revealed an area of ulceration in the nasopharynx (Wassermann reaction, negative). This condition persisted for a week before gradually subsiding, but the patient's general state had meantime undergone grave deterioration. About the middle of November bleeding from the gums ceased, as did the appearance of subcutaneous haemorrhagic spots. Some improvement of general condition set in,

and although still far from well he was allowed to leave hospital at his own request early in December. During his stay in hospital his treatment consisted of pepsac, one ounce daily, with liver twice weekly: no blood transfusions were given.

Patient had only been at home for a few days when he developed gastro-enteritis, with severe diarrhoea, which was followed on December 16th by the

Table XV. *Differential white count.*

Date	Red blood cells millions	Hb	White blood cells	Poly-morphs	Lympho-cytes	Mono-cytes	Eosino-phils	Baso-phils
15 Aug.	4·00	75	2200	—	—	—	—	—
4 Oct.	2·60	82	1900	23·9 (449)	73·3 (1391)	1·6 (30)	1·0 (19)	0·6 (11)
	Red blood cells regular in size and shape: polychromasia +. One nucleated red cell seen. Reticulocytes 7 %.							
14 Oct.	4·00	—	1500	21·4 (321)	76·3 (1145)	1·3 (19)	1·0 (15)	0·0
	Red blood cells showed considerable irregularity of size and shape: polychromasia +. A few nucleated red cells seen.							
28 Oct.	4·32	70	1775	13·2 (235)	85·0 (1509)	1·0 (18)	0·7 (13)	0·0
	Polychromasia +. Two nucleated red cells seen. Reticulocytes 3 %.							
11 Nov.	3·30	72	2400	5·3 (127)	93·8 (2251)	0·7 (17)	0·2 (5)	0·0
	Red blood cells irregular, some macrocytic. Polychromasia +. Two nucleated red cells seen (normoblasts).							
18 Nov.	4·35	90	2400	3·0 (86)	96·6 (2304)	0·4 (10)	0·0	0·0
	Red blood cells irregular in size and shape. Polychromasia +. Fourteen nucleated reds seen (7 megaloblast, 7 normoblast). Platelets almost completely absent. Occasional cells of myeloblastic type noted.							
28 Nov.	4·32	90	2600	3·7 (96)	95·7 (2488)	0·5 (16)	0·0	0·0
	Red blood cell irregular in size and shape. Polychromasia +. Punctate basophilia +. Six nucleated red cells seen. Platelets scanty.							
9 Dec.	4·34	65	5400	5·0 (270)	90·0 (4860)	5·0 (270)	0·0	0·0
	Red blood cells irregular in size and shape. Polychromasia +. Six nucleated red cells seen. Platelets few.							
23 Dec.	2·21	50	1200	5·5 (67)	94·4 (1133)	0·0	0·0	0·0
	Red blood cells fairly regular. Polychromasia +. Ten nucleated red cells seen. Platelets numerous. Lymphocytes of large type.							

onset of a pneumonic condition. The pneumococcus isolated from his sputum did not belong to types I, II or III. He was re-admitted to hospital, but his condition was very grave and he died on December 24th.

At autopsy there was found to be an area of consolidation in the lower lobe of the left lung. Though the illness had run seven days the patch was still at the stage of red hepatisation, with no evidence of leucocytic infiltration. There

was slight (terminal) degeneration of the muscle of the right heart. The spleen was engorged, but showed no abnormality of size or consistence. There was also engorgement of para-vertebral lymph glands, but no abnormality of kidneys, liver or other organs was noted on macroscopic examination.

Marrow from rib and femur was taken for microscopic study, as well as pieces of lung, spleen, kidney and abdominal lymph gland.

Organs.

Only some of the tissues were available for examination, but these showed interesting features.

Bone marrow (Pl. figs. 1–5). This was taken from the shaft of the femur and was a red marrow. On microscopic examination it was found not to be a very cellular marrow but to consist of capillaries full of erythrocytes. The general tissue matrix was oedematous or gelatinous and contained finely granular cytoplasmic debris. In some parts there were very few cells to the tissue matrix and yet the marrow was not the usual fatty tissue of the medulla of a long bone. In other parts, the majority, there were a fair number of cells consisting of normoblasts, a larger number of undifferentiated reticulum cells and megakaryocytes. The large relative proportions of blood capillaries to marrow parenchyma was noteworthy. When the gelatinous matrix is looked at carefully it is seen to be cellular with the cells fading out (cytolysis). The megakaryocytes are unlike those of a normal marrow. Their variation in size from a quite small cell to a large one is noteworthy: nuclei may be 2 to 12 in number. Some of these instead of having the usual convoluted basket nucleus look like foreign body giant cells. Again the nucleus may be pycnotic or fragmented or composed of discretely distributed elements or badly staining. As regards the truly myeloid type of cell, ranging from myeloblast to myelocyte, it was difficult to be certain that these types were really present. No granulocytes were seen. Mitoses were not found. One had the impression with examination, that in spite of being truly a red marrow, this was really a marrow in a state of aplasia and no longer manifestly haemopoietic.

Lymphatic gland (Pl. figs. 9–16). The gland examined was from the abdominal cavity. Its architecture was greatly changed in the direction of a reticular cell proliferation which, while rendering the sinuses very prominent, also spreads beyond them to medullary cords. Actual germinal centres are absent, the lymphoid tissue is diffusely distributed over follicular and medullary cord regions and there is considerable replacement and permeation of the lymphoid tissue by reticular cells. The sinuses are distended with large and somewhat eosinophilic cells. Mitoses are present in considerable number among the reticular cells. Both a fibrosis and a reticulosis are to be made out. Apparent phagocytosis of erythrocytes can be made out in the sinuses, but no very evident phagocytosis of blood pigment. The apparent erythrophagy, however, may be and probably really is a vacuolation. In addition there are degenerative changes in the large reticular cells producing bizarre forms.

Plasma cell types, some of them bi-nucleated, are present in small numbers. There is no indication of a myeloid metaplasia.

Spleen. There appears to be a marked diminution of Malpighian bodies, which present an ill-defined appearance at their periphery. Lymphocytes are rather loosely aggregated. The pulp generally shows an endothelial or reticular cell appearance and is somewhat bloodless. Cells generally in the pulp appear to be undergoing cytolysis. Mallory's stain brings out the pulp cords to be made up of prominent reticulin and faintly staining cells. Phagocytosis of blood pigment could be made out. That there is a considerable amount of haemosiderosis is brought out by the Prussian blue reaction, mostly intracellular but also diffuse. The fibrous trabeculae and capsule are very prominent, hyaline in appearance and almost acellular. The arterioles within the Malpighian bodies have very hyaline walls. Some mitosis are present in the cells of the pulp. With fat stain there could be made out some ordinary fat cells in groups in the trabeculae but also numerous single large cells full of fat all over the pulp area, which have the appearance of phagocytes.

Kidney. Some fibrosed glomeruli are present and one focus of lymphocytic aggregation. There is no sign of albuminous fluid in Bowman's capsule. The epithelium of tubules is rather necrotic and granular in appearance and some of these tubules are dilated with a coagulum in the lumen. Staining with Sudan IV shows up the glomerular endothelium, tubular epithelium and the tubule casts all to be fatty. There is no marked change of general architecture.

Lung (Pl. figs. 6–8). The appearance of the lung is very peculiar. Its alveoli are filled with blood and blood fluid and there is no indication of cellular reaction. Not a polymorphonuclear leucocyte could be seen anywhere. It is a pure haemorrhagic solidification, a simple red hepatisation. Isolated masses of micro-organisms (? pneumococci) are present, which may possibly have been due to an increase post-mortem. The walls of the alveoli are very congested. No polymorphs are to be seen in blood contained in the larger blood vessels. The section stained with Mallory's connective tissue stain shows up especially—in blue coloration—the large amount of serous fluid in the alveolar spaces and the large amount of orange coloured blood in the capillaries of the alveolar walls. The application of a fat stain (Sudan IV) showed fatty granulation throughout the entire wall of the larger blood vessels and also affecting the endothelial inner lining. A fine fatty granulation is also present in the endothelium of the capillary blood vessels. Alveolar epithelium too is fatty and there are free cells within the alveolus which contain small fat droplets.

Commentary.

This case only presented symptoms in the last $2\frac{1}{2}$ years of his life. A history of a marked trauma complicates the judgment to be made whether these symptoms were those of toluene poisoning. This man was a noted athlete. The possibility of his being a bleeder seems unlikely. Moreover it was not merely nose bleeding and headache which were his only symptoms. He had evidently

had haemorrhages in other parts of the body and especially renal haemorrhage which could scarcely be attributable to nose trauma. The petechial character of the haemorrhages, which were apparent on the tongue and face, were very suggestive of the establishment of a purpuric diathesis. His blood condition too was a strong argument for a poisoning of the benzene type. The condition can be described as an agranulocytic anaemia—agranulocytic to a high degree—for, with a total of only 1200 leucocytes on the last occasion when he was examined, he had only 5·5 per cent. of polymorphs to 94·5 per cent. of lymphocytes. That he might have been a case of a primary blood disease cannot absolutely be ruled out, but with an occupation known to produce a disease of the type here met with, an especially healthy man with no syphilitic and no hereditary taint, and conformity of the symptoms and post-mortem appearances to the descriptions given of benzene and toluene poisoning, we may conclude that there is a very high probability that this was such a case. That it was a case of idiosyncrasy, that is to say one in which factors representing a special sensitivity, constitutional or induced, also seems probable. Still this may not amount to more than saying that poisoning with toluene is exceptional, or at least the amount of poisoning which matters. There seems no reason to doubt that if the industrial poisoning be conceded in this case it was due to toluene and not to benzene.

VII. Discussion and summary.

In our investigation of our subject we have perused the literature, analysed the data of other workers, conducted a number of animal experiments, considered the bearings clinical and pathological of a case of presumed toluene poisoning, and conducted an investigation into the blood state and symptoms of co-workers with this case and yet are unable to give a categorical answer to the question. What are the relative toxicities of toluene and benzene? We would almost feel inclined to echo the words of another worker in the experimental field with regard to benzene, Neumann (1915), who concludes: "The fact that my results so often do not correspond either with one another or with those of Selling, so often indeed do not correspond to expectation, justifies the conclusion that, although benzene is to be regarded as a powerful leucotoxin, it manifests great individual differences in its mode of action and it is very difficult to lay down exactly what action is to be expected."

We should be inclined to put the case somewhat differently however and put forward the following view as our tentative finding.

The actions of benzene and toluene are very similar. That of benzene is the more powerful because it is a more volatile substance and can therefore reach higher concentration than toluene. This greater volatility at the same time is a reason why it is eliminated more quickly and its effects are less lasting than those produced by toluene. The action of both these substances is on young body cells, probably whatever they are and wherever they may be found, but is most easily discoverable because of its action on the young bone marrow cell

and the consequent effect on the cells of the peripheral blood. It is not a specific action but operates, according to circumstances, on the stem cells of the myeloid leucocyte or the erythrocyte. This does not mean that the substances have little or no effect on the lymphocyte, for the lymphoid tissue in the body is so very abundant that it would only be in extreme cases that the effect on that cell would be manifest peripherally. Like many poisons, indeed like many of the drugs which are used in Medicine, the first effects of these substances are stimulating. Leucocytosis, erythrocytosis and possibly thrombocytosis are early manifestations or the manifestation of slighter action, with histological evidence of hyperplasia. This is succeeded by the truly toxic or destructive action and the production of leucopenia, anaemia, thrombopenia and the effects due to action on other organs. The ultimate result in clinical terms is an agranulocytic anaemia accompanied by purpura haemorrhagica and, as the pathological manifestation an aplastic bone marrow. The fatal termination is commonly an infection to which there is no resistance possible in an individual deprived of defence cells and possibly also of defensive substances in the body fluids. Powerful solvents of fat as both these chemical substances are, they produce an action through this means also, on nerve cells, capillary endothelium and parenchyma of organs with consequences represented in nervous symptoms and in haemorrhages. This then is our reading of the results of our investigation and explanation of the variability which may be found, a variability which is regarded mainly as one of phase, although we do not exclude idiosyncrasy altogether as explanation.

VIII. Conclusions.

Toluene is a poison of the same type and action as benzene, but acts less readily because of its physico-chemical properties. It may possibly and under certain circumstances have a more lasting effect due to slower elimination.

Acknowledgments.

We desire to express our thanks to Dr J. C. Bridge, H.M. Senior Medical Inspector of Factories, for his help in the preparation of this report, and to Dr Goodall for allowing us to keep in touch with the patient when under his hospital care.

REFERENCES.

Adler-Herzmark, J. and Selinger, A. (1930–31). *Arch. Gewerbepath. u. Gewerbehyg.* **1**, 763.
Batchelor, J. J. (1927). *Amer. J. Hyg.* **7**, 276.
Chassevant, A. and Garnier, M. (1903). *C. R. Soc. Biol.* **55**, 1255.
Englehardt, W. E. (1931). *Arch. Gewerbepath. u. Gewerbehyg.* **2**, 479.
Fuhner (1921). *Biochem. Ztschr.* **115**, 235.
Hamilton, A. (1931). *Arch. Path.* **11**, 434, 601.
Harvey, W. F. and Hamilton, T. D. (1932). *Edin. Med. J.* **39**, 285, 349.
Henderson, Y. and Haggard, H. W. (1927). *Noxious Gases.* New York, pp. 164–5.

HERTZMANN, O. (1931). *Arch. Gewerbepath. u. Gewerbehyg.* **2**, 515.
JAFFE, R. H. (1932). *Arch. Path.* **14**, 177.
KLIENEBERGER, C. and CARL, W. (1912). *Die Blutmorphologie der Laboratoriumstiere.*
LEHMANN, K. B. (1909–10). *Arch. Hyg.* **71–72**, 30.
MAYER, S. (1931). *Arch. Gewerbepath. u. Gewerbehyg.* **2**, 516.
MAYERS, J. (1928). *J. Ind. Hyg.* **9**, 305.
MITNIK, P. and GENKIN, S. (1931). *Arch. Gewerbepath. u. Gewerbehyg.* **2**, 457.
NEUMANN, W. (1915). *Deutsche med. Woch.* **41**, 394.
PAPPENHEIM, A. (1914). *Ztschr. exper. Path. u. Ther.* **12**.
PEARCE, L. and CASEY, H. E. (1930). *J. Exp. Med.* **51**, 83.
RAMBOUSEK, J. (1911). *Gewerbliche Vergiftungen.* Leipzig. Transl. T. M. Legge. 1913.
SANTESSON, C. G. (1897). *Arch. f. Hyg.* **31**, 336.
SCHRIDDE, H. (1908). *Cbl. allg. Path. u. path. Anat.* **19**, 865.
SELLING, L. (1911). *Ziegl. Beitr.* **21**, 556.
—— (1916). *Johns Hopkins Hosp. Rep.* **17**, 83.
SMITH, A. ROSS (1928). *J. Ind. Hyg.* **9**, 73.
STOCKE, A. (1929). *Zbl. Gewerbehyg. u. Unfallverh.* **16**, 355.
WEISKOTTEN, H. G., GIBBS, B. F., BOGGS, E. O. and TEMPLETON, E. L. (1919–20). *J. Med. Res.* **41**, 425.
WORONOW, A. (1929). *Virch. Arch.* **271**, 173.
WURM, E. (1931). *Arch. Gewerbepath. u. Gewerbehyg.* **2**, 766.
ZANGGER, H. (1930). *Ibid.* **1**, 77.

EXPLANATION OF PLATES VIII AND IX.

Fig. 1. Bone marrow. *a*, general tissue matrix, oedematous or gelatinous. *b*, fat cell of marrow. *c*, marrow cells, degenerating and undergoing cytolysis. Many of the cells in the photograph are red blood cells and normoblasts. × 170.

Figs. 2 and 3. Bone marrow. *a*, normoblasts. *b*, reticulum cells. *c*, megakaryocytes, of unusual appearance. *d*, blood capillaries. No myeloblasts, myelocytes, nor granular cells to be made out. × 300 and × 900.

Figs. 4 and 5. Bone marrow. *a*, normoblasts. *b*, reticulum cells. *c*, megakaryocytes, quite unlike those of normal marrow and varying both in size and number of nuclei. × 900.

Fig. 6. Lung. Mallory stain. *a*. alveoli filled with blood and blood plasma. *b*, masses of blood fibrin. *c*, large distended blood vessels, which contain erythrocytes only and not a single polymorph. × 100.

Fig. 7. Lung. Mallory stain. Alveoli filled with blood. *a*, blood plasma and *b*, fibrin. *c*, very congested alveolar walls. Erythrocytes show up white. × 600.

Fig. 8. Lung. Haematoxylin and eosin. *a*, enormous mass of blood plasma. *b*, erythrocytes. *c*, alveolar wall. *d*, fibrin. No indication of any polymorphonuclear leucocytes. × 600.

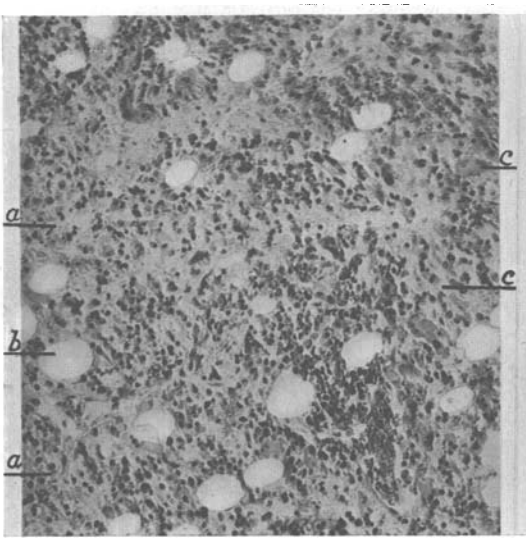
Figs. 9 and 10. Lymph node. *a*, reticulum cells showing degenerative changes. *b*, gland capsule. *c*, lymphocytes. × 170.

Figs. 11, 12 and 13. Lymph node. *a*, reticulum cells showing marked degenerative changes, vacuolation and cytolysis. *b*, monster and multinucleated reticulum cells. *c*, cytolytic debris. *d*, lymphocytes. × 300.

Figs. 14, 15 and 16. Lymph node. *a*, reticulum cells showing marked degenerative changes, vacuolation and cytolysis. *b*, monster and multinucleated reticulum cells. *c*, cytolytic debris. *d*, lymphocytes. *e*, mitotic figures. *f*, large cell with suggestion of phagocytosed contents. × 900.

N.B. regarding magnifications: Owing to exigencies of space, all of the original photomicrographs had to be reduced by one-eighth for reproduction. We however let the magnifications stand as given for the microphotographs supplied by the authors.—ED.

(*MS. received for publication* 5. VII. 1933.—Ed.)



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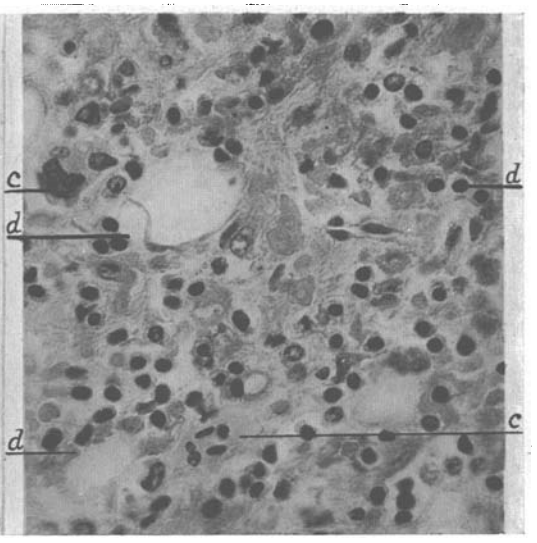

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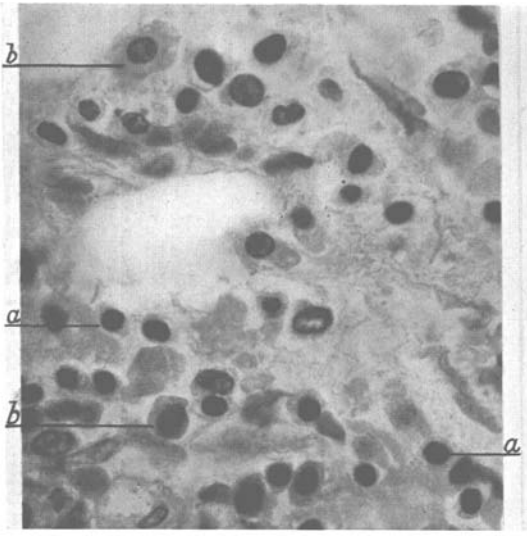

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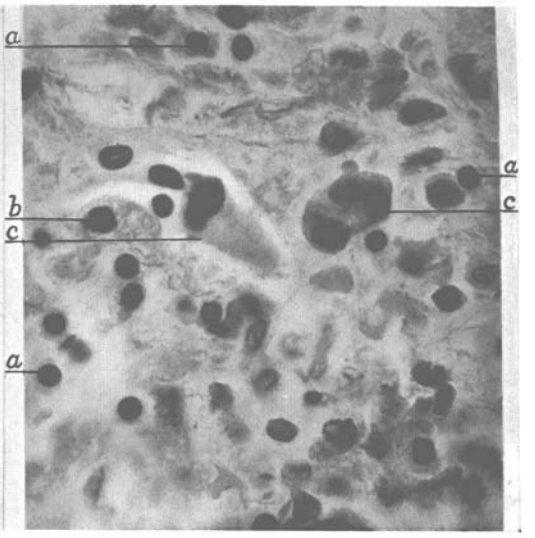

Fig. 4.

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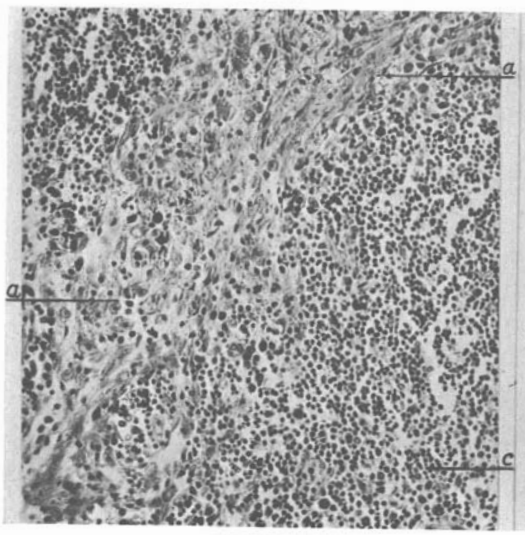
PLATE VIII



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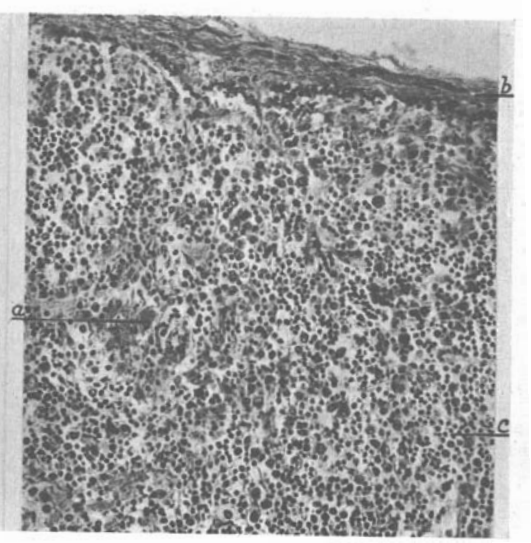

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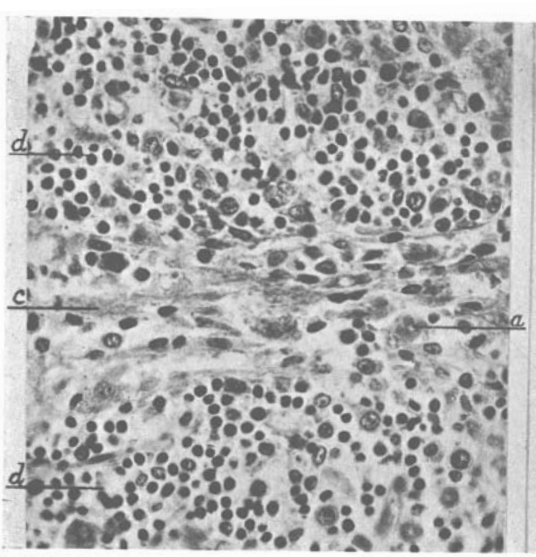

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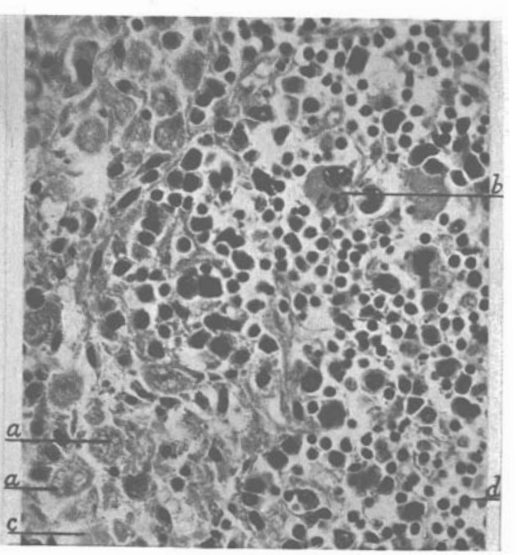

Fig. 8.

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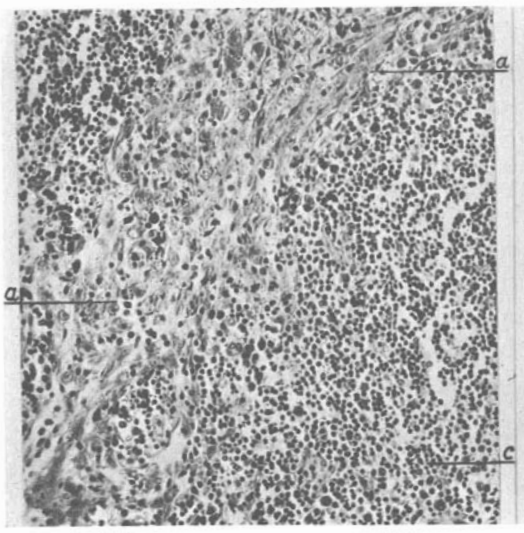

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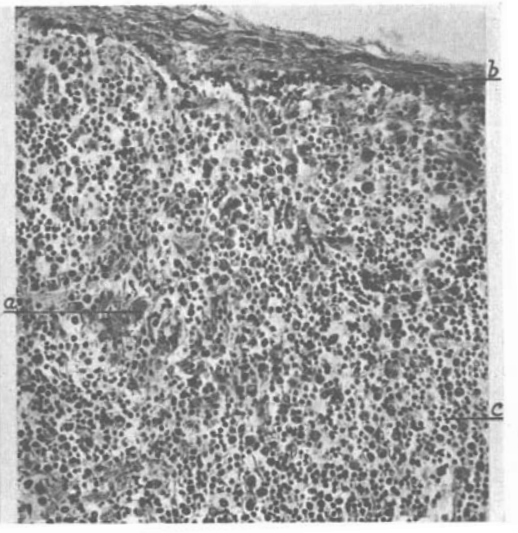

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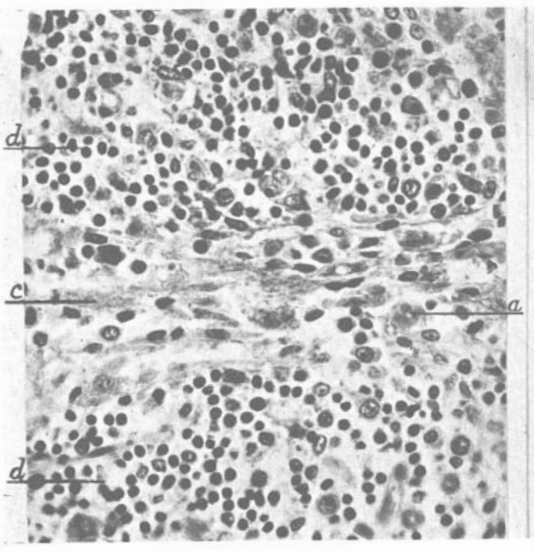

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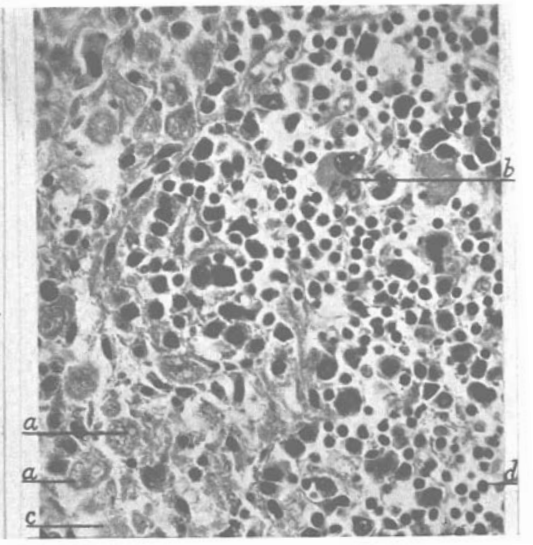

Fig. 12.

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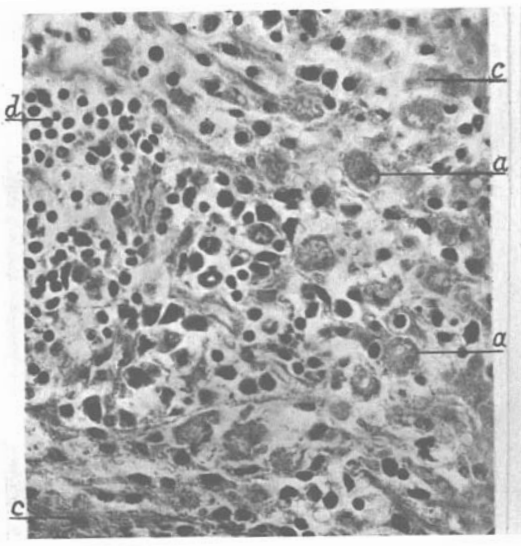

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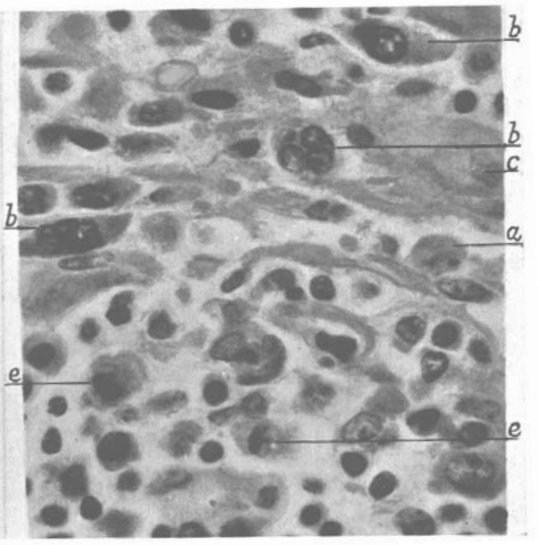

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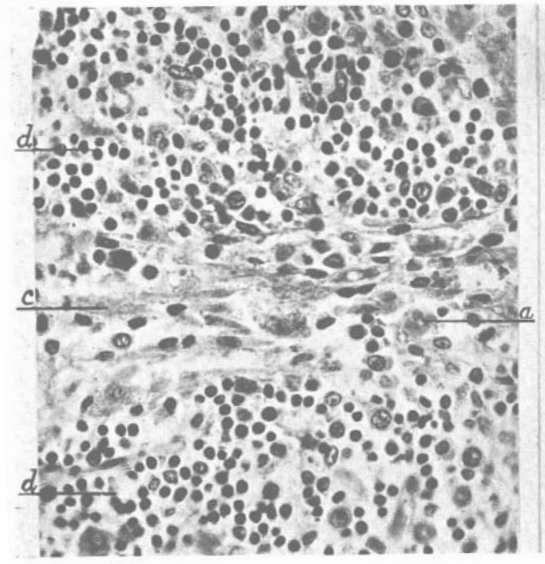

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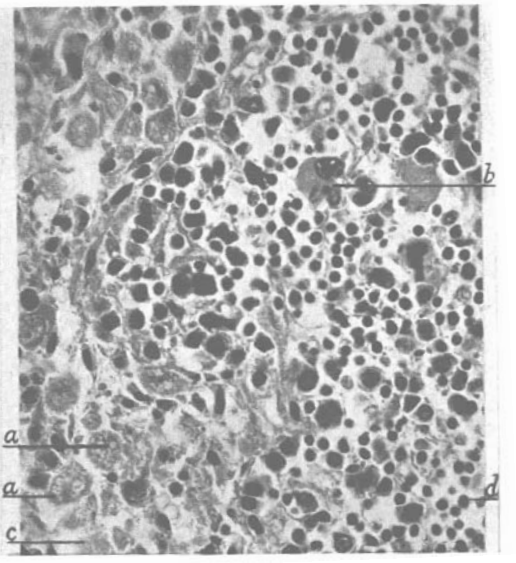

Fig. 16.

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