MEDICAL RESEARCH COUNCIL
INDUSTRIAL HEALTH RESEARCH BOARD

REPORT No. 80

TOXICITY OF INDUSTRIAL ORGANIC SOLVENTS

SUMMARIES OF PUBLISHED WORK

Compiled by Ethel Browning
under the direction of the Committee on
The Toxicity of Industrial Solvents

LONDON
HIS MAJESTY'S STATIONERY OFFICE
1937

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PREFACE

In response to a request from the Home Office for a scientific investigation into the possibility of various volatile substances having injurious effects upon the health of workers using them under industrial conditions, the Medical Research Council appointed the special Committee of which the constitution is shown on the opposite page.

There are many such substances used in industry, chiefly as solvents, and the number is increasing. It is known that some of them are dangerous to inhale under certain conditions, i.e. where the vapour is concentrated in an enclosed space: how dangerous has on several occasions not been realised until a fatal accident has occurred. What is not well known is which of these many compounds might be suspected before use as being dangerous—and which are, in fact, harmless. Moreover, a substance which causes acute toxic symptoms when breathed in high concentration may be suspected of having some injurious effect on health when inhaled in a less concentrated form over a long period: whether this occurs, and if so what organs of the body may be specially affected by such chronic exposure, is not known.

There was thus a clear need for research into the possible effect of substances that seem open to suspicion, either through having a chemical constitution closely allied to that of compounds already proved to be dangerous or through complaints of ill-health among those who constantly use them. As a first step, however, it was plainly desirable to take stock of existing knowledge of the subject.

Much has been written in this and other countries about the effects on health of the solvents commonly used in industry, but no attempt seems to have been made to collect the information in one volume for reference. At the Committee's request, therefore, Dr. Browning has made the following summary of the available literature. Although it is not exhaustive, it is for practical purposes sufficiently full to show the extent of the problem, to indicate the most suitable points of attack, and to serve as an aid to those investigators whose task it will be to work in this field of experiment.

To the large body of makers and users of solvents in the chemical and allied industries the report should be of special interest. It, therefore, seemed to the Medical Research Council that the Report Series of their Industrial Health Research Board was a fitting medium of publication.

TOXICITY OF INDUSTRIAL ORGANIC SOLVENTS

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ETHEL BROWNING, M.D.

Under the direction of the Committee

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ABBREVIATIONS

Metre,	m.	Cubic metre,	c.m.
Centimetre,	cm.	Cubic centimetre,	c.c.
Millimetre,	mm.	Cubic millimetre,	c.mm.
Micron,	μ	Boiling Point,	B.P.
Kilogramme,	kg.	Boiling Range,	B.R.
Gramme,	g.	Flash Point,	F.P.
Centigramme,	cg.	Melting Point,	M.P.
Milligramme,	mg.	Specific Gravity,	Sp. Gr.
Litre,	l.	Molecular Weight,	Mol. Wt.
Millilitre,	ml.	Parts per Million,	p.p.m.

INTRODUCTION

(By the Committee)

The following report comprises extracts from all the existing information that could be obtained as to the effects on animals and man of the various solvents used in industry. The literature from which the extracts were compiled is widely scattered in various reports and scientific periodicals. Thus, whilst much trouble has gone towards their compilation, completeness of the references cannot be vouched for: moreover, new work is being published at frequent intervals. Only in exceptional instances, therefore, is work published after December 1935 included. The main objective in the collection and publication of these data is the avoidance of poisoning from the industrial use of such solvents, and the indication, where possible, of methods of prevention. Under present conditions of industry it is often difficult to determine, should illness occur in a worker or group of workers, whether or not this is due to the toxic action of chemical agents, and, if so, which particular agent is responsible. This difficulty is often increased by the slow development of symptoms which may occur after prolonged or intermittent exposure to low concentrations. The direct method of determining the possible and relative toxicity of a substance in man is by experiments with that substance on man himself, under conditions as nearly as possible parallel with those under which a worker is exposed to such substance. Experiments on man are not justified: recourse must, therefore, be had to experiments on animals in the laboratory, and for various reasons such experiments provide only indirect, though usually very relevant, evidence of the probable action of these substances on man.

Determinations of toxicity involve the use of a large number of animals. Owing to expense and the difficulties of housing large animals preliminary investigations are nearly always made on small animals. Unfortunately no general rules can be laid down which relate the sensitivities to poisons of small rodents and of man. There are, further, many poisons which produce completely different effects in different species of animals. It is, however, very exceptional for a substance which is toxic to various species of rodents to be innocuous to man, and vice versa. It is to be anticipated that there will exist qualitative and quantitative differences in response to any poison between man and the lower animals, just as they are known to exist between different species of lower animals themselves. Nevertheless there can be no doubt that experiments on small animals are of value by giving an indication of the type of toxic action as well as the relative toxicity of the substance under investigation. Thus the fact that butyl cellosolve (ethylene glycol mono-*n*-butyl ether) is five times as toxic to mice as ethylene glycol at least gives a warning that the former compound may have greater potential dangers for man than the latter.

In attempting to translate ascertained effects on small animals to probable or suspected effects on man, certain factors have to be taken into consideration. The first of these is the size of the animal. As regards the systemic actions of poisons, depending as they do mainly upon the concentration of the poison which occurs in the blood and tissues, it is generally true that a given amount of poison will produce greater effects in a small than in a large animal. No entirely satisfactory method is known for correlating accurately dosage and body weight, but a useful approximation is obtained by the usual method of stating the dosage as per kilogramme of body weight. From what has already been said in regard to the differences in response between different species of animals, it will be readily understood that, if the minimum lethal dose of a solvent for a rat, weighing 0·2 kilogrammes, is 1 c.c., it does not follow that the corresponding dose for a man weighing 70 kilogrammes, will be 350 c.c. It must also be remembered that even such an approximate relation does not hold good for the local effects of poisons, before they are absorbed. For example, a given concentration of a volatile solvent in air may produce local effects on the lungs, the intensity of which bears no relation to the weight of the animal.

Apart from the difficulty of variation of effect by species, a factor of outstanding importance is the individual variation shown in response to drugs. This subject has been extensively investigated and it is now known that individual variation is found with all drugs and in all populations of animals. Measurements of toxic effects on animals usually express the average or median toxic dose or concentration, i.e. the quantity that produces the observed effect in half the population studied. Unfortunately the range over which individual variation is scattered differs widely in the case of different drugs. Some individuals will be less, some more, sensitive to a toxic action than the majority. This is of especial importance in human beings when it is necessary to avoid producing toxic effects on any particular individual. There is in addition the important question of exceptional sensitivity or idiosyncrasy to poisons. Recently it has been found, for instance, that certain drugs which have been widely used for many years without apparent danger, can nevertheless produce in certain exceptional individuals very serious toxic effects. It is possible that cases of personal idiosyncrasy would occur with all drugs though they may be only recognised with those that are widely used. Similar cases of idiosyncrasy will no doubt arise from the use of substances in industry, and where slight signs of intoxication occur with any new solvent this should consequently be regarded seriously even if other individuals have sustained greater exposure without any apparent injury.

Consideration of the available literature on the actions of solvents has shown that many experiments have been made with little direct relation to the conditions that may possibly occur in industry. For example, the effect of the subcutaneous injection of a large dose

of substance may be entirely different from, and have little bearing upon, the effects which may be produced by prolonged inhalation of small quantities. The Committee had some hesitation in including an account of such experiments, but in the case of some substances they were the only experiments available. They have therefore been included partly for completeness and partly for such evidence as they afford. It is hoped, however, that arrangements will be made in future for carrying out animal experiments which will be more directly related to the conditions in industry in which exposure to risks of poisoning occur.

One other difficulty requires mention. The number of chemical compounds used as solvents is large, but unfortunately the number of proprietary names is much larger, and a toxic substance may be concealed under such a name. It has not been possible to give a glossary of proprietary names, and this report will only be of service in judging the safety of a solvent in those cases where the chemical composition of the solvent is known.

From what has been said above, it is obvious that the bibliography contained in the following pages must rapidly become out of date and require periodical revision.

Finally, a word is due to the carefulness and thoroughness of the author, who has been at great pains to consult every available source of information.

CHAPTER I. THE HYDROCARBON GROUP

1. Benzene

(*Benzole*)

C_6H_6, i.e. 

Properties

Benzole, or benzene, a hydrocarbon of the aromatic series, and a coal tar product, is to be carefully distinguished from benzine, a mixture of varying and uncertain proportions of hydrocarbons chiefly hexane and heptane), which is a distillate of petroleum.

A certain amount of confusion has arisen from time to time in reports of cases of toxic injury due to " benzine ", e.g. the case of fatal aplastic anaemia in a cellulose sprayer in 1934, in which the toxic agent was referred to in the Lancet as benzine, when benzole was meant. Simonin (1934) points out that the distinction between benzene and benzine is not merely of theoretical importance. He quotes as an instance the occurrence of a severe collective intoxication in a boot factory in 1932, involving 44 workers, 8 of whom died, caused by the misinterpretation of an order for " benzine ", benzene being delivered instead (see also Merklen and Israel, 1934).

The effects of chronic poisoning by the two substances, especially with regard to the blood picture, are clearly distinguishable, while the acute narcotic effect of benzine on animals has been shown to be less than half that of benzole. (Bamesreiter, 1932.)

It has been suggested by some French workers, notably Duvoir (1922), that benzine should be called " petrol essence " and that the word benzinism should be replaced by " petrolism ".

Benzole is graded commercially as crude or refined, according to the percentage which distils below 100°C, "*Pure*" benzole should be the pure substance strictly designated as *benzene* (C_6H_6). B.P. 80°C, Sp. Gr. 0·884 at 15°C. M.P. 5°C., soluble in water to the extent of 0·2 per cent. An excellent solvent for rubber, gums, resins and fats of all kinds. *Commercial benzole* is practically never pure ; it contains traces of xylene, toluene, phenol, thiophene, carbon disulphide, acetonitrile, probably (according to Ellis and Meigs, 1921) pyridine, and many other substances. (For method of analysis see Gooderham (1935).) A process for removing thiophene by the action of acidified hypochlorite solution, with only a small attendant loss of benzole has recently been described by Ardagh and Bowman (1935). The three usual commercial types are :

(*a*) *Commercial crystallisable*—100 per cent. benzene. B.R. 80–81°C. Sp. Gr. 0·882. This variety appears to produce very severe toxic effects, many cases of poisoning having been reported from its use. A typical example is the series recorded by De Balsac, Heim and Agasse Lafont (1933), of which 8 were fatal, and by Merklen

and Israel (1934) who describe their cases as "haemorrhagic aleukaemia" from the use of crystallisable benzene. These workers urge that the use of crystallisable benzene should be prohibited.

(*b*) *Commercial 90 per cent. benzole.*—90 per cent. by volume distils below 100°C. It contains 13–15 per cent. toluole, 2·3 per cent. xylole, and sometimes as impurities traces of olefins, paraffins, sulphuretted hydrogen, and other bodies.

(*c*) *50 per cent. benzole*—contains 50 per cent. of constituents distilling below 100°C. and 90 per cent. below 120°C.—a highly mixed product.

The usual *commercial 90 per cent. benzole* is a colourless mobile refractile liquid, with a not unpleasant odour. It burns with a luminous but smoky flame; it is extremely volatile, especially if slightly heated. Its relative time of volatilisation compared with that of ethyl ether is 3 : 1 (I. G. Farbenindustrie). It is a good solvent for a number of cellulose esters and ethers, especially ethyl cellulose, also for most oils, and for ester gums, benzyl abietate, copal ester, cumarone, benzyl resin, and many other resins. It does not dissolve cellulose acetate or nitrate, copal, or shellac.

Manufacture

Benzole is given off during the distillation of coal in a closed vessel, part remaining in the tar and part in the gas. The chief means of recovery is by "stripping" the benzole from the coke oven gas, a method which has of recent years largely superseded distillation of the tar from gas works and coke ovens. During 1934, of the total production of crude benzole at coke ovens, gas works, low temperature carbonisation works and tar distilleries, about 80 per cent. was obtained from the gas and 20 per cent. from distillation of tar (Report of Secretary of Mines, 1934, H.M. Stationery Office).

A full description of the distillation method was given by Lehmann (1911) and of the "stripping" process in the Report of the National Safety Committee on Benzole (1926).

Uses

The use of benzole received a great impetus during the War, but since that time its extension has been wide and rapid. While in 1922, 68 million gallons were used in America, in 1928 the figure had reached 115 millions (McCord, 1929).

Benzole may be regarded as having two more or less distinct fields of application to industrial processes:

(*a*) Where it is handled in large quantities in closed mechanical systems. This branch includes:

(i) *The distillation of coal and coal tar* in the production of benzole;

(ii) *The blending of motor fuels.* It is noteworthy that according to Pfeil (1932) cases of poisoning reported from the exhaust gases of machines in which benzole is used as a motor fuel are not actually due to benzole but to carbon monoxide, since exhaust gases contain no benzole.

(iii) *The chemical industries*, including oil extraction, dye and dye intermediates, manufacture of paints, varnishes and stains, and of paint and varnish removers.

(*b*) Where it is used as a solvent or diluent. This branch includes :

(i) *The rubber industry*—in solutions for " rubber cement " in the manufacture of straw hats, cardboard boxes, waterproof goods, shoes, cameras, the sealing of cans, the rubber tyre industry, etc.

Four cases of poisoning, two of which were fatal, from the use of shoe cements containing a large proportion of benzole, were reported by Hunter and Hauflig in 1927. With regard to the sealing of cans, Hamilton (1931) remarks that since the introduction in 1926 of rubber latex as a substitute for rubber dissolved in benzole, many works have substituted latex for the benzole rubber sealing mixture, but that no less than one-third of all food cans are still sealed with benzole.

In the manufacture of rubber tyres, benzole is also used extensively ; the metal case on which the tyre is built being usually coated with rubber cement in which considerable quantities of benzole are used. It was in tyre building that 5 cases (3 fatal) of benzole poisoning with aplastic anaemia and haemorrhages occurred, which were described by Harrington in 1917. A series of cases of poisoning, 6 deaths, 12 severe and several slighter cases, occurred in a rubber factory in Vienna in 1932, although all the apparatus used was of the closed type. The trouble apparently arose from the transportation of goods moist with benzole from one room to another. (Fischer, 1932.)

It is noteworthy that in an Austrian Government Order of May 1st, 1934, prohibiting workers in processes utilising benzole, toluole, xylole, trichloroethylene, etc., from working more than 4 hours a day (and, when large quantities are used, more than 2 hours a day), the processes covered by the more stringent restrictions include the cold vulcanisation of rubber and the production of rubber substitutes.

(ii) *In artificial leather manufacture.*

Textiles are spread with a coating of a viscous liquid consisting essentially of nitrocellulose and castor oil dissolved in ethyl acetate or other suitable solvent, benzole in amounts up to 60 per cent. being added as a diluent. Two of the 6 cases of benzole poisoning reported by Hunter and Hauflig, and a fatal case mentioned by Hamilton (1928), occurred in the manufacture of patent leather.

(iii) *In the dyeing and cleaning industry*—for degreasing, mordanting and removal of grime from clothing and other articles, also generally for cleaning purposes in workshops. In many dyeing and cleaning establishments, however, other solvents have largely replaced benzole.

(iv) *In the paint and varnish industry*—as a diluent for lacquers ; as a constituent of quick drying paints* ; in bronzing and gilding pottery ; in varnishing reservoir vats, ships, motor cars, etc. ; in floor and woodwork stains and floor waxes. In connection with quick drying paints, it is emphasised by Flury and Zernik (1931) that the use of benzole is attended with special danger from the fact that it volatilises quickly from the painted surface, especially when the surface is warm, as in metal parts of machines, or when the paint is sprayed on. Details of the conditions and risks of this process are given by Smyth and Smyth (1928) summarising the findings of the Department of Labour and Industry in Pennsylvania (1926) and of the National Safety Committee on Spray Coating (1927). It was finally recommended by the Committee that no lacquers be used for spraying which contain over 0·5 per cent. of benzole.

(v) *In the aviation industry*—as a constituent, to the extent of about 20 per cent., of the " dope " solution. An investigation by Kranenburg and Peters (1928) of workers in an aeroplane factory showed great and

* Very little benzole is used at the present time in the manufacture of paints, varnishes and lacquers, and it is only used to a slight extent in paint and varnish removers.

characteristic changes of the blood picture in a large number. In one case, after 6 years' exposure, there was a relative lymphocytosis of 62 per cent. and a reduction of haemoglobin to 65 per cent.

(vi) *In the linoleum and celluloid industries.*

(vii) *In artificial manure and glue manufacture.*

(viii) *In electrical fitting and accumulator works.*

(ix) *In chemical laboratories*—attention has been drawn by Bloomfield (1928) to the possibility of poisoning in laboratories where tests are conducted with rubber, paint, varnish and oil products and involve centrifuging with benzole the material to be tested. He found a considerable amount of benzole in the air of such laboratories—28 to 223 parts per million—and examination of workers revealed in 3 cases a change in the ratio of polymorphonuclear leucocytes to lymphocytes.

(x) *In the alkaloid industry*—for the extraction of atropine, hyoscine, codeine, etc. Nine cases of chronic benzole poisoning in workers in this industry were reported by Mitnik and Genkin (1931).

Concentration of Benzole Vapour in Air of Factories

The actual concentrations of benzole in air to which workers have been exposed have been found to vary greatly. The earliest figures, given by Lehmann (1911), ranged from 25 to 106 parts per million of the air in benzole washing and distillation plants. Legge (1920) found the quantities in the atmosphere of a balloon fabric spreading room to range from 210 to 1,050 p.p.m. in different parts of the room, and in a pneumatic tyre manufacturing room from 800 p.p.m. with an exhaust fan in operation to 2,800 p.p.m. with the windows open. In a Milan raincoat factory, where three fatal cases occurred, Pugliese (1922) found 1,000 p.p.m. In the National Safety Council Report of 1926 examination of the air of 18 different workrooms, representative of the various processes in which benzole is used in rubber, artificial leather, wire insulating, dry cleaning, and sanitary can manufacture, revealed a very wide variation of its benzole content—from 0 to 4,140 p.p.m. (the latter in a dry cleaning process during the summer when no other solvent than benzole was used). It should be noted that the method used for the estimation of benzole in the survey failed to distinguish between benzole and other solvent vapours such as alcohol, methyl acetone, etc., but the figures for solvent vapours were all computed in terms of benzole. These studies brought out the importance of local exhaust ventilation in reducing the atmospheric content of benzole. The Report concludes that "rooms in which benzole is evaporated into the air without local exhaust ventilation will in most cases show high concentration of the fumes in the air of the rooms—With ideal local exhaust ventilation on the other hand even large quantities of benzole can be used without heavy atmospheric contamination". After the occurrence of two fatal cases in Edinburgh, in 1918, it was found that without ventilation the concentration of benzole in the room reached 16,800 p.p.m., and with 30 changes of air per hour was reduced to 550 p.p.m.

Risk of Explosions due to Benzole Vapour

The vapour of benzole (F.P. 10°F.) forms an explosive mixture with air in proportions from 5 per cent. to 8 per cent. Escape of the vapour or liquid may occur through faulty design of the plant or faulty ventilation, and ignition may be produced by the presence of naked lights, the production of sparks by the use of tools or appliances such as electric fans, motors, etc., or by iron-shod boots on stone floors, trolley wheels, etc. Precautions to avoid these dangers are described in the Chemical Works Regulations 1922 Reg. 4. b, also in Safety Circulars 29, 43 and No. 51 of the Association of British Chemical Manufacturers, 1931, and in Quarterly Safety Summary, 1930, 1931.

Concentration of Benzole in Air in Relation to Toxic Effects

The maximum allowable concentration, above which toxic symptoms may be expected to occur, was estimated by the National Safety Council (1926) as 100 p.p.m. The concentration which produces fatal results in a very short time appears to be 19,000—20,000 p.p.m. In the report made by Mr. McNair to the Home Office on a fatal case of benzole poisoning occurring in 1930 he states that to form a mixture which would be fatal would require 2 volumes in 100 of air, representing 7 oz. weight of benzole per 100 cubic feet. He also states that 1 volume per cent. can be recognised by smell, while Safety Circular No. 51 (Association of British Chemical Manufacturers 1931) states that more than 1 mg. per l. (0·029 per cent.) is necessary before the smell is distinctly perceived.

The following table of concentrations of benzole according to their effects and time of exposure is taken from the table drawn up in " Mechanical Engineering " (1935).

Concentration of benzole vapour in air (p.p.m.).	Effects.
19,000	Fatal in very short time.
3,000	Dangerous with exposures of ½ to 1 hour.
3,130 to 4,700	Maximum concentration for exposures of ½ to 1 hour.
1,570 to 3,130	Slight symptoms with exposures of several hours.
100	Maximum concentration allowable.

Estimation of Benzole Content of Air

Numerous methods for the determination of the amount of benzole in air have been described. The majority of the earlier ones are reviewed by Tausz (1924) and include the nitrification method, introduced by Harbeck and Lunge (1898), used by Lehmann (1910) and adapted by Smyth (1931) for concentrations as low as 30 p.p.m, and the method of activated charcoal considered superior to all others by Tausz himself, and used by the National Safety Council in 1926. Two more recent methods have been described by Ficklen and Cook (1933) and Cook and Ficklen (1935); the former, the

" pernitric " method, they have since found not applicable because of the interference of toluene; the latter, the oxidation method with peroxide in presence of iron salts, will be described below.

The following is a brief résumé of the chief methods which have been used :—

(1) *The nitrification method*, as adapted by Smyth (1931). The method described by Smyth (1929) consisted in catching the benzene vapours in a mixture of sulphuric and nitric acids, neutralising, separating the dinitrobenzene formed in the acids by steam distillation (from a buffered solution when toluene was present in the air) and then titrating the nitro compound with titanous chloride. This method was shown to be 93·1 per cent. correct for pure benzene vapour at 11,000 p.p.m. and 99·2 per cent. correct at 200 p.p.m. In order to adapt the method for concentrations as low as 30 p.p.m., Smyth (1931) took larger samples of air for analysis than formerly, so as to obtain enough dinitrobenzene for titration. He found the method 99–100 per cent. correct with pure benzene vapours at concentrations of from 30–585 p.p.m., even in the presence of various aliphatic alcohols and acetates. In the presence of not more than three times as much toluene as benzene, the accuracy was over 85 per cent. down to a concentration of 30 p.p.m. of benzene.

It is pointed out by Cook and Ficklen (1935) that the method requires transportation of air samples to a central laboratory for determination of the amounts of benzene present. A modification of it is, however, described by Schrenk, Pearce and Yant (1935) by which small samples of air can be used and as little as 0·001 mg. of benzene can be determined.

(2) *The activated charcoal method*, as used by the *National Safety Council* (1926). Special precautions to render the sampled air moisture-free before passing it into the charcoal absorption tube consisted in the provision of a first tube filled with soda lime for the absorption of acid vapours and a second with calcium chloride for absorption of water vapour. The charcoal tube itself contained approximately 7 g. of 8–14 mesh activated charcoal. The charcoal was also dried overnight in a constant temperature oven at 105°C. The charcoal tubes were equilibrated before use by the passage of compressed air, flowing at the rate of approximately 6 litres per minute, through a chain composed of the following elements :—Cotton wool tube, soda lime tube, calcium chloride tube, glass tubing manifold and six charcoal tubes. A sample of the air of the workroom, usually 20 litres in amount, was aspirated through the prepared charcoal, and the increase in weight of the charcoal was taken to represent the approximate amount of solvent vapours in the atmosphere sampled. Where benzole is the only solvent used, this increase in weight represents that due to benzole vapours only, but since the charcoal absorbs other solvent vapours also, the method is not specific for benzole.

(3) *The oxidation method with hydrogen peroxide in presence of iron salts.* (Cook and Ficklen, 1935.) In this method the air to be sampled is streamed at the rate of 2 litres per minute on to the surface of glass beads in a U-tube packed round with solid carbon dioxide; the tube is later removed and immersed in hot water, when the collected benzene is volatilised, passed through a bubbler unit containing 25 ml. of water for the removal of the more water-soluble vapours, and thence into a trap immersed in a solid carbon dioxide and acetone cooling bath, the benzene and a small portion of less water-miscible solvents being frozen out in the trap. For the estimation of the benzene, 5 ml. of 0·5 per cent. ferrous sulphate followed by 2 ml. of 1 per cent. hydrogen peroxide are directed down the inlet tube of the trap, the contents of which are then shaken and transferred to a test tube. If benzene is present in an amount of 0·005 ml., a characteristic brown coloration is produced in 2 to 5 minutes; if in amounts of 0·010 ml. to 0·050 ml., a black amorphous precipitate in addition. Upon the addition of 1 ml. of 2*N* nitric acid the black amorphous precipitate will dissolve and the solution may then be diluted with water and compared with standards in a colorimeter.

A number of other solvents, having boiling points relatively near that of benzene (toluene, xylene, methanol, ethyl acetate, trichloroethylene, carbon tetrachloride, cellosolve, acetone, etc.) were tested, and did not give the reaction when no benzole was present. Carbon disulphide gave a greenish amorphous sulphur precipitate, which, if benzole is being simultaneously estimated, must be filtered from the solution after the addition of nitric acid, the benzole being then estimated from the coloration of the filtrate.

Ficklen and Cook (1933) observe that, owing to the complicated nature of the reaction, the method is only approximately quantitative, but sufficiently so to permit estimation of the concentration of benzene in air within the limits required in an industrial hygiene investigation.

(4) *The Interferometer.*—Data on the use and worth of this instrument are supplied by the United States Bureau of Standards, and by the current catalogue of the Arthur H. Thomas Co. (West Washington Square, Philadelphia). It is stated (Reply to Query, *J. Amer. med. Ass.*, 1935) that the instrument is of restricted value under many industrial circumstances, owing to the fact that benzene, benzine, naphtha, toluene, and xylene are rarely used as single entities, but as mixtures with various esters, acetates, alcohols and glycols. This fact precludes any ready standardisation of the apparatus to meet the diversity of vapour conditions likely to be encountered.

Acute and Chronic Benzole Poisoning

It is clearly apparent, both from the study of cases of benzole poisoning in human beings, and from experimental work on animals that acute and chronic benzole poisoning are two entirely distinct phenomena.

" In acute benzole poisoning the symptoms are due to a severely irritant and destructive effect upon the central nervous system, whereas in chronic benzole poisoning the relatively slight effects on the central nervous system are not at all comparable with the severity of the degenerative changes occurring in the haematopoietic system. In acute poisoning benzole thus acts as a convulsive neurotoxin and later as an asphyxiant narcotic " (Batchelor, 1927).

Chronic poisoning presents a wide variety of subjective symptoms, both in number and in degree of severity, but the occurrence of any two of these, together with the cardinal symptoms of leucopenia, is regarded as being sufficient to confirm the toxic effect of exposure to benzole (McCord, 1929). The criterion of benzole poisoning from the blood picture, as the result of the investigations by the National Safety Committee on Benzole (1926) and the New York and Pennsylvania Commissions on Spray Painting (1927) are as follows :—

Leucocyte count below 5500 (average normal 7500).

Reduction of neutrophils to less than 60 per cent.

Anaemia (reduction of red blood corpuscles and of haemoglobin) is of less importance and may be absent in the earlier stages (Mitnik and Genkin, 1931).

Absorption and Excretion of Benzole in Animals

Absorption

(*a*) *Absorption through the lungs.*—Rabbits, according to the investigations of Lehmann (1910) have a smaller capacity for absorption of benzole through the lungs than human beings. Whereas men absorbed 80 per cent. of the benzole vapour inhaled, rabbits

absorbed only 63 per cent. No definite ratio between the relative amount absorbed and the total amount present in the air was found.

(*b*) *Absorption and distribution in the body tissues and fluids.*—According to Yant and co-workers (1936) the United States Bureau of Mines has carried out experiments which show that the absorption of benzole from the blood takes place with remarkable rapidity, a matter of minutes being significant. They have also found that fatty tissues have a special predilection for benzole, the concentration in the bone marrow being in some cases 20 times that in the blood. From a recent account of a post-mortem investigation of a man who died of acute benzole poisoning, by Koppenhöfer (1935) this would not appear to be the case in human beings (see below, Toxic Effects in Man, p. 34).

(*c*) *Absorption through the skin.*—The investigations of Lazarew and co-workers (1931) have shown that benzole in the form of vapour, as well as in liquid form, can be absorbed through the skin of animals. In liquid form, benzole produced great irritation. Immersion of the ears of rabbits for 2½ to 3 hours was followed by inflammation and oedema, then by pus formation and finally mummification of the ear, while immersion of the whole body of a mouse was followed after about 3 hours by death, probably due to irritation of the skin.

When the bodies of the animals were kept in a chamber filled with benzole vapour, the heads being passed through an opening so that no inhalation of the vapour was possible, no general symptoms of intoxication were observed. Evidence of absorption through the skin, however, was obtained in 3 ways :—

(1) by estimation of the hydrocarbon content of the air expired by tracheotomised rabbits with one foot immersed in benzole. The estimation was carried out by the method of Matmejew, Pronin and Frost (1930), which consists briefly in the decomposition of the benzole vapour into carbon dioxide and water in an electric oven, and " automatic conductometric " titration of the carbon dioxide with caustic soda. The benzole appeared in the expired air after 3–4 minutes in amounts of 1·2 to 1·5 mg. per l., the total amount expired in the course of 115 minutes' immersion of the foot being 138 mg. The speed of absorption of benzole through 1 sq. centimetre of skin was therefore calculated as more than 0·016 mg. per minute (0·013 to 0·76 mg. in a later investigation by Lazarew and co-workers (1931)).

(2) by the estimation of phenol (as an oxidation product of benzole) in the urine. The urine of animals kept as described above in a chamber filled with benzole vapour showed a strong phenol reaction (Mellon's re-agent).

(3) by the concentration of benzole in the blood. The amount of benzole in the blood of rabbits after immersion of the ear in benzole was estimated by Lazarew, Brussilowskaja and Lawrow (1931) and the average amount during 30 minutes' immersion plotted as a curve, which rose to between 50 and 100 mg. per kg. of blood taken from the external jugular vein.

Lazarew and co-workers correlate the absorption of benzole through the skin with its water-solubility as well as its fat-solubility. They estimate its water solubility as 0·033 to 0·040 g. per l. and explain its greater speed of absorption as compared with that of benzine by the lower water solubility of the latter (0·007 to 0·015 g. per l.).

Excretion

While the greatest amount of benzole is excreted unchanged by the lungs, a certain amount is oxidised in the body and excreted in the urine in the form of phenol, monoxybenzene, dioxybenzene, pyrocatechin, hydroquinone and muconic acid (Jost, 1932). In animals the excretion of benzole in the urine has usually been estimated by the amount of phenol excreted. The phenol excretion of rabbits after 2 hours' daily inhalation of benzole in a concentration of 13·6 mg. per l., has been estimated by Sartorius and Sudhues (1933). The average phenol excretion rose almost immediately from a normal level of 2 mg. per day to 50 mg., and later to nearly 100 mg. When inhalation was stopped the phenol excretion sank to the normal level only after 4 or 5 days. This finding appears to indicate, according to Sartorius and Sudhues, that many cell systems must constitute special storage centres for benzole.

Change in sulphates in urine of animals exposed to benzene. Some recent investigations by Yant, Schrenk, Sayers, Howath and Reinhart (1936) show that a change in the normal ratio of inorganic to organic sulphates (i.e., a decrease in inorganic sulphates) in the urine is a constant and early sign of benzene poisoning in animals. The analysis of urine specimens from 79 dogs exposed to concentrations of from 100 to 800 p.p.m. of benzene vapour for periods of 100 to as long as 1,000 days in one instance showed that a rapid and marked decrease occurred in the percentage of inorganic sulphates of the total sulphates in the urine. Single examples of their figures will suffice to show the quantitative aspect of this decrease.

Concentration of Benzene (p.p.m.)	Daily exposure (hours).	Exposure period (days).	Percent. of Inorganic sulphates.	
			Before exposure (average).	After exposure (average).
100	8	42	89·4	57·0
500	8	317	94·7	28·8
800	1	17	86·7	62·5
800	8	192	96·5	6·3

A distinct decrease in the percentage of inorganic to total sulphates occurred even with conditions of exposure which did not produce anaemia or leucopenia. With conditions which produced benzene poisoning a great decrease occurred weeks and months in advance of anaemia, leucopenia and the common signs and symptoms of benzene poisoning. The mechanism of the response is

believed to be due to oxidation of the benzene to phenol or phenolic derivatives, which in turn are conjugated in the liver with sulphate ions to form ethereal sulphates, thereby causing a shift to the right in the system: inorganic sulphates $\rightleftharpoons$ conjugated sulphates. The shift or decrease in inorganic sulphates is related quantitatively to the severity of the exposure to the point of complete elimination of the inorganic sulphates.

Acute Toxic Effects in Animals

It has long been known that benzole in large doses produces in animals a severe narcosis, often accompanied by symptoms of irritation of the central nervous system (tremor, muscular twitching, etc.), and, if in doses above the minimum lethal dose, followed by death. Until recently it was believed that the cause of death was invariably respiratory paralysis, but some investigations by Nahum and Hoff (1934) suggest that, although death may occur from respiratory failure during the stage of narcosis, it may also occur suddenly from myocardial failure produced by the action of benzole, both by causing the liberation of adrenaline and at the same time sensitising the myocardium to its toxic action.

The acute effects of benzole on animals have been studied from results of intraperitoneal injection and of inhalation. The symptoms arising from irritation of the central nervous system are essentially similar in both modes of administration, but the intense effect is most apparent when benzole is administered intraperitoneally, owing to its rapid absorption.

Intraperitoneal Injection

The *lethal dose* for guinea-pigs was found to be 0·73 c.c. per kg. body weight (Chassevant and Garnier, 1903); but Batchelor (1927) found the lethal dose for rats to be between 1·5 and 1·75 c.c. per kg.

The *symptoms* of profound tremor and muscular convulsive twitchings were obtained with doses as low as 0·25 c.c. per kg. body weight, and in addition a definite narcotic effect, with drowsiness, instability of gait, impaired equilibrium, weakness, paresis-decreased susceptibility to pain stimuli, and cessation of voluntary movement. As the spinal cord was affected, loss of reflexes resulted.

Post-mortem findings.—Batchelor observed intense acute congestion of the peritoneum and abdominal viscera, with much fibrin deposit on these surfaces; considerable sero-sanguinous intraperitoneal exudate; injection of the gastric mucosa with small haemorrhages and ulceration, and acute congestion of the lungs. No appreciable effect was noted on the blood cell count.

Inhalation

In large doses, the effect of inhalation of benzole vapour upon animals is that of a nerve poison, with a characteristic neuro-irritant effect, as evidenced by muscle twitching, convulsions, general tremor (compared by Bénech (1897) to that of paralysis agitans), a state of hypertonicity of the body and musculature (Batchelor, 1927),

shown in many cases by a peculiar rigid S-shaped formation of the tail (Lazarew, 1929).

A toxic action upon the heart is also postulated by Nahum and Hoff (1934), progressive anoxaemia of the myocardium, and a sensitisation of the myocardium to the effects of adrenaline, so that death may occur from ventricular fibrillation. Different species of animals vary in their susceptibility to acute benzole poisoning, the rabbit being more resistant than the mouse (Lehmann, 1912), while the cat appears to have a special sensitivity (Lederer, 1932; Engelhardt, 1931).

According to Lehmann and others, animals of the same species, especially cats, also show a great variation in individual susceptibility, death occurring sometimes with relatively small dosage and short exposure, while on the other hand feeble animals receiving large doses may show only slight weakness and others may recover from severe narcosis. It appears from the work of Nahum and Hoff (1934) that some of these individual susceptibilities may be explained by variations in adrenaline response; periods of hyperexcitability being accompanied by increased liberation of adrenaline, to the action of which the myocardium is already sensitised by the action of benzole.

The *lethal and narcotic concentrations* are given in the following table:—

Animals.	Lethal concentration.		Narcotic concentration.		Author.
	mg. per l.	p.p.m.	mg. per l.	p.p.m.	
Mice	45	14,000	—	—	Lazarew (1929).
,, ...	—	—	38	12,000	Fuhner (1921).
Cats	170	53,000	60	19,000	Lehmann (1912).
,, ...	—	—	730	9,500	Bamesreiter (1932).
Dogs ..	146	46,000	—	—	Luig (1913).
Rabbits ..	46 (after 2 hours)	14,500	—	—	Lehmann (1912).

The onset of acute symptoms is apparently at concentrations ranging from 15 mg. per l. (4,700 p.p.m.) for mice to 22 mg. per l. (7,000 p.p.m.) for cats (Bamesreiter, 1932).

The following table, from Lehmann (1912), shows the progress of events with different concentrations in rabbits:—

Concentration mg. per l.	Parts per million.	Time of exposure.	Convulsions after.	Lateral position after.	Light narcosis.	Deep narcosis.	Further progress.
37	12,000	5 hrs.	2½ hrs.	35 mins.	—	5 hrs.	Slow recovery.
46	14,500	3 hrs.	1 hr. 20 mins.	—	—	2 hrs.	Death after 3 hrs.
92	29,000	70 mins.	9 mins.	9 mins.	40 mins.	50 mins.	Slow recovery.

(It should be noted here that the results obtained by Bamesreiter (1932) with regard to the narcotic symptoms produced by inhalation of benzole vapour by cats give a toxicity greater than that found by Lehmann. Lehmann, in a note appended to Bamesreiter's article, observes that the discrepancy is due to the fact that Bamesreiter has used a modification of the original "Würzburger" apparatus, the new "Ludwigshafen" apparatus, described by Gross and Kuss (1931).)

Bamesreiter's results are summarised as follows :—

Lateral posture	..	above	22	mg.	per l.,	6 hours'	exposure.
Light narcosis	..	,,	28	,,	,,	,,	,,
Deep ,,	..	,,	30	,,	,,	,,	,,

Post-mortem findings.—The organs of animals dying from inhalation of lethal concentrations of benzole vapour have not shown any specially characteristic changes ; in a few cases haemorrhage of the lungs has been observed. The most outstanding feature was the fact that the blood remained fluid for a long time after death (Beinhauer, 1896 ; Lehmann, 1912 ; Heffter, 1915). No microscopic changes in the blood were found in Lehmann's animals ; an odour of benzene could be detected in the lung cavity if opened promptly after death.

Chronic Toxic Effects in Animals

Both by subcutaneous injection and by inhalation experiments on animals the toxic effects of benzole have been investigated and described by a large number of workers beginning with Langlois and Desbouis (1907), Lehmann *et al.* (1910) and Selling (1916). It was chiefly Selling's extensive experiments, carried out by subcutaneous injection, that led to the clear conception of benzole as a leucotoxin, destroying not only the circulating leucocytes in the blood, but also the parenchymatous cells of the bone-marrow, spleen and lymph glands. The destructive effect, he observed, was more pronounced on the myelocytic than the lymphatic elements. In addition Selling's experiments brought out the following points : a less obvious effect on erythrocytes, due to injury of the erythoblastic tissue in the bone-marrow : an initial stimulating effect on the bone-marrow with a resulting initial leucocytosis : regeneration of the injured tissues when removed from the influence of benzole.

In essentials these results have been confirmed by more recent workers, but in some cases the details have not been reproduced. Thus Ferguson, Harvey and T. D. Hamilton (1933) were not able in rats and rabbits to produce a well-marked neutropenia with less effect on the erythrocyte system. In fact anaemia was even more evident than leucopenia, and an erythropoietic disturbance was even more manifest in the peripheral blood picture than a leucopoietic. According to a statement made by A. Hamilton (1934) these findings of Ferguson *et al.* are characteristic rather of the usual findings in human beings suffering from benzole poisoning than of those observed by most workers with experimental animals. Hamilton states that animal experiments do not show the destruction of red blood

corpuscles which in human beings is often more conspicuous than the destruction of white corpuscles.

The discrepancy may be explained by the opinion expressed by Ferguson *et al.*, and their agreement with a statement made by Selling which has been less emphasised than the main results of his investigation. Selling observed 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 production of granulocytes, nor to the loss of red blood cells solely by the production of erythroblasts." The conclusion of Ferguson *et al.* appears to be a confirmation of this observation. They state " 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."

This appears also to be the opinion of McCord, Cox and Boyle, as the result of the extensive survey embodied in their report to the Industrial Health Conservancy Laboratories in 1932. Their general conclusions as to the toxic effects of benzole on animals may be summarised as follows :—Leucopenia is not a consistent feature of benzole poisoning in animals and is not pathognomonic of it. No pathognomonic features absolutely characteristic of benzole poisoning are to be found in life or *post mortem*. Concentrations of 5 parts of benzole per 1,000 of air have set up signs of intoxication in rabbits equal to or more severe than 10 parts per 1,000. All grades of benzole, whether or not containing impurities, such as thiophene, carbon disulphide or acetonitrile, exert a toxic action on rabbits.

Some of the intoxication produced in animals both by subcutaneous injection and by inhalation, cannot strictly be labelled " chronic," since the doses used led immediately to more or less acute effects.

In Batchelor's (1927) experiments, for example, doses of 1 c.c. per kg. body weight were injected on successive days, and in some cases untoward general symptoms appeared early and resulted finally in death. The inhalation experiments of Ferguson *et al.* similarly can scarcely be regarded as illustrative of chronic poisoning, for the effect was acute and the exposure had to be short in order to avoid the death of the animal. These workers themselves suggest that in this fact lies 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. Batchelor's inhalation experiments, however, included the inhalation of lower as well as higher concentrations of benzole (from 2,440 p.p.m. down to 460 p.p.m.), and, while no symptoms, except weakness, anorexia, and loss of weight, resulted from concentrations of 800 and 460 p.p.m., definite injury to the haemopoietic and excretory organs was produced by these lower concentrations.

The inhalation experiments of Lederer (1932) on dogs are of special interest in this connection, since dogs are apparently

considerably less sensitive than other species to benzole poisoning, and Lederer was able to carry on the investigation over a period of 2½ years with daily inhalations of 6 hours of concentrations of 7 to 10 mg. per l. (2,200 to 3,100 parts per million).

Symptoms of Poisoning by relatively Small Amounts of Benzole

The symptoms of poisoning by relatively small amounts of benzole in animals are slight—weakness, anorexia, and loss of weight. Even when, as in the case of Lederer's dogs, symptoms of nervous instability appear at the beginning of the experiment (tremor, muscular hypertonicity, restlessness) tolerance appears to be fairly rapidly established, with the disappearance of gross pathological manifestations.

Lesions of the Bone-marrow and Internal Organs

Bone-marrow.—Both in the more acute and in the strictly chronic intoxications, the changes in the bone-marrow are essentially those leading to aplasia affecting all cell types, but the appearances differ in individual animals according to whether preliminary stimulation or regeneration has taken place. Thus, in some of the animals investigated by Engelhardt (1931) (inhalations of 10–25 mg. per l.; approx. 3,000–8,000 p.p.m.) the bone-marrow showed very little change; in some there was degeneration and destruction of leucocytic elements, and in others irritative phenomena—new red cell formation, immature leucocytes, etc.

The regenerative phase has perhaps been best described by Selling in his original "ascending" series of animals.

> The regenerative process in the bone-marrow begins with the formation of small, circumscribed cell groups and islands, composed of large lymphocytes, granulocytes or erythroblasts. In any given island, after cellular differentiation has once begun, the type of cell, whether erythroblast or granulocyte, remains constant. The islands increase in size and number, fuse with each other, and lead to a complete filling of the reticulum with parenchymal elements. In the earliest stages the younger cell types (myeloblasts and megaloblasts) are relatively abundant. In the later stages these cells are still present, but in comparison with more highly differentiated cells they are relatively scarce.

These reparative changes have been further emphasised by Heitzmann (1931) who describes a preliminary atrophy of the bone-marrow followed by a hyperplasia, especially of the leucocytic elements, in animals subjected to subcutaneous injection. Heitzmann, however, lays particular stress on the destruction of leucocytic elements in the bone-marrow as the characteristic effect of chronic poisoning by inhalation of benzole.

In Schillowa's (1933) experiments with rabbits receiving subcutaneous injections of benzole the characteristic lesion of the bone-marrow was hyperplasia, chiefly of pseudo-eosinophils, megakaryocytes and erythroblasts.

Spleen.—The characteristic injury to the spleen appears to be aplasia (atrophy of Malpighian corpuscles and stroma) with

pigmentation and increase in connective tissue, but myeloid metaplasia and hyperplasia have also been observed.

Selling (1916) and Brandino (1922) recorded the occurrence of myeloid metaplasia as a regenerative phenomenon. In the more acute cases of intoxication in animals examined by Ferguson *et al.* (1933) no indication of myeloid metaplasia and no evidence of haemosiderin deposition were found, but in the animals subjected to chronic inhalation by Engelhardt there was much deposition of blood pigment in the spleen, and Heitzmann, who examined them, states that this indicates a toxic action of benzole on the red blood corpuscles. Lignac (1932) who claims to have produced acute leukaemia in mice by injection of small doses of benzole, states that while the myeloid tissue in the spleen undergoes destruction, the lymphoid tissue is increased (hyperplasia follicularis lienis). Schillowa (1933) on the other hand, emphasises as the characteristic change in rabbits injected with benzole, a marked hyperplasia of the reticulo-endothelial elements, especially the endothelial sinuses, and describes the formation of rhombic crystals, analogous to Charcot-Leyden crystals, as the result of phagocytosis of eosinophils.

Liver.—Among the earlier workers, Pappenheim (1913) reported the presence of a parenchymatous hepatitis, but this was not confirmed by others (Monckeberg, 1913; Neumann, 1915, etc). In Batchelor's experiments the liver showed evidence of injury and focal necrosis with inhalation of concentrations as low as 815 p.p.m., but in Lederer's dogs the liver injury was comparatively slight, affecting chiefly the reticulo-endothelial cells, and in Engelhardt's cats and rabbits the chief changes were congestion and deposition of haemosiderin.

Kidneys.—Among the earlier workers only Pappenheim observed injury of any severity in the kidneys, while according to Batchelor's (1927) investigation, injury is slight with inhalations of low concentration; he observed cloudy swelling and tubular casts only with 440 and 815 p.p.m. McCord, Cox and Boyle (1932), however, lay great emphasis on nephritis as an outstanding characteristic. They state that the special point of attack is the convoluted tubule lying between the Malpighian corpuscle and the beginning of Henle's tubule.

Bladder.—McCord, Cox and Boyle also state that inflammatory conditions of the bladder, in which large numbers of pus cells may be present in the urine, are of fairly frequent occurrence in animals poisoned with benzole.

Gastro-intestinal tract.—Inflammatory reactions of the stomach and other parts of the intestinal tract are also recorded by McCord and co-workers. They state that in the stomach these reactions are preceded by purpura of the mucous membrane and may be followed by the formation of ulcers.

Thymus.—According to Lewin (1928) benzole produces, in rabbits, atrophy of the thymus, the histological changes being those of "accidental involution". An increase of interlobular connective

tissue is accompanied by the new formation of a network of collagenous bundles within the lobules. Regeneration is possible only if complete " inversion " of the gland has not taken place.

Lymph glands.—Only slight hyperplasia with pigmentation and phagocytosis was found with fairly high concentrations (Batchelor, 1927), though Brandino (1922) recorded a notable destruction of lymphocytes. Schillowa (1933) noted a diminution of lymphoid tissue and phagocytosis of pseudo-eosinophils but no nuclear pyknosis or necrosis of the lymphoid nodules.

Lungs.—Lesions of the lungs—catarrhal bronchitis, emphysematous areas, decrease in the lymphatic tissue and thrombosis of vessels—have been described by Schmidtmann (1930); pneumonic processes, bronchial catarrh of a desquamative nature and commencing cirrhosis of the lung by Mgebrow (1930); and fatty emboli and emphysema by Schillowa (1933).

Brain.—Degenerative processes in the vessels of the brain cortex and in the ganglion cells have been reported by Amenossow and Blinkow (1929).

Action on the Circulatory System

Paralysis of the vasomotor system, with resultant rapid lowering of the blood pressure, is recorded as an effect of benzole poisoning in animals by Dautrebande (1933, 1935) and Dautrebande and Waucomont (1933), after inhalation of benzole vapour through the trachea. These workers believe that the site of action of benzole is upon the muscle fibre of the peripheral vessels, not on the nerve endings. Their opinion is supported by experiments with fragments of isolated organs (heart, intestine, ureter), which when placed in Ringer's solution containing benzole, immediately cease contraction (Dautrebande and Waucomont) and by the negative results obtained on applying known peripheral vasomotor stimulants (adrenaline, ephedrine, pituitrin) after benzole (Dautrebande, 1935).

On the heart, according to Litzner (1932) benzole produces progressive diminution of contraction, especially of the ventricles, while Dautrebande (1935) states that benzole inhalation produces bradycardia, which appears even during the occlusion of the two common carotids. This bradycardia is always increased by injection of adrenaline or hordenine, and after adrenaline benzole intoxication may produce a fatal syncope by ventricular fibrillation. This conclusion can be well correlated with the results of Nahum and Hoff (1934) on the acute effects of benzole poisoning in animals (see p. 16).

Effect on the Alkali Reserve

According to Cavagliano (1932) no change takes place in the alkali reserve (estimated by the method of van Slyke) of animals in which the characteristic blood changes have been produced by chronic inhalation.

Changes in the Blood

The results of innumerable experiments on animals, mostly by subcutaneous injection of benzole, have, on the whole, confirmed Selling's original observation that the striking and characteristic effect of benzole poisoning is a reduction of leucocytes. The essential fact brought out by later researches, especially by those of Wallbach (1929, 1931) and of Weiskotten and co-workers (1915–1930) and others is that the toxic action affects all forms of leucocytes rather than being specifically toxic to granulocytes. The striking effect on granulocytes is not so much their depression as the appearance of immature forms (Hunt and Weiskotten, 1930; Weiskotten 1930). In the later stages the red blood cells and platelets are also involved, and it is from these two marked differences between the condition of the blood in benzole poisoning and in true agranulocytosis that a conception of the mechanism of benzole poisoning has been evolved. This subject is discussed by McCord (1929), Dameshek (1929), Kracke (1932) and Kracke and Parker (1935) (the latter has claimed to have produced true agranulocytosis in animals by subcutaneous injections of benzole) but the present position appears to be that summarised in the opinion of Reznikoff and Fullerton (1933) :—

> This "shift to the left" may be due to an attempt on the part of the bone-marrow to compensate for leucocytic destruction or to depression of maturation. The fact that bone-marrow studies do not show any hyperplasia and do show some depression for the most part indicates that the depressing action of benzole is on the formative and maturative function of the marrow in addition to any possible leucolytic effect . . . In addition to eventual involvement of the red blood cells and platelets which is present in true granulocytopenia, the striking predominance of immature polymorphonuclears during the period of progressive leucopenia when benzole is administered suggests a different mechanism from that taking place during granulocytopenia. It may be that granulocytopenia affects primarily the formative functions of the granulogenic elements of the marrow and perhaps the delivery of granulocytes from the marrow into the circulation; whereas benzole injures the maturative as well as the formative function.

Susceptibility to benzole poisoning in animals of different species and of the same species. Many of the discrepancies in the findings of different workers in animal experiments are apparently to be ascribed to both individual and species susceptibility. Thus Wallbach (1931) was unable to produce in guinea-pigs and white mice the characteristic leucopenia obtained under similar conditions in rabbits, and states (1933) that only in man, dogs and rabbits is leucopenia an invariable result of benzole poisoning; other animals are refractory to the action. He also points out that underlying constitutional conditions, especially infection (e.g., infection at the site of injection of benzole solutions) may have a considerable effect on the leucocytic response.

Schillowa lays special emphasis on the individual susceptibility of animals of the same species, as judged by the blood picture and the degree of bone-marrow injury. He states that in the benzole-susceptible animal leucopenia and thrombopenia occur, with an aplasic condition of the bone-marrow and necrobiotic changes in the

granulocytes. In less susceptible animals the blood picture shows little change, while the bone-marrow may show considerable hyperplasia of myelogenous tissue.

It has already been observed that cats have been found to show a special sensitivity to acute poisoning by benzole. According to Sartorius and Sudhues (1933) they are not suitable for investigation of the results of chronic benzole poisoning because they are liable even with comparatively small doses by inhalation to develop symptoms of irritation of the respiratory tract, leading to secondary infection and purulent broncho-pneumonia.

In the earlier investigations constant results were only obtained by subcutaneous injections. Thus, while Langlois and Desbouis (1907) recorded a definite diminution of leucocytes and increase in erythrocytes after inhalation of benzole vapour, Luig (1913) obtained " practically negative " results with chronic inhalation of 5–10 mg. per l. Later investigations, however, by Weiskotten and co-workers (1920), Engelhardt (1931), Batchelor (1927), etc., have shown that the typical leucopenia observed after subcutaneous injection can be reproduced after inhalation, though, according to Engelhardt, to a smaller degree.

The results obtained by Ferguson, Harvey and Hamilton (1933), either by injection or inhalation, do not present the picture of a well-marked neutropenia, with less effect on the erythrocyte system, recorded by many workers. These workers tentatively explain the variability of their results as " one of phase," owing to the fact that the toxic action of benzole is not a specific action but operates according to circumstances on the stem cells of the myeloid leucocyte or the erythrocyte. The somewhat similar results obtained by Beyer (1933) in which the picture was that rather of a terminal anaemia preceded by a leucocytosis than of a definite leucopenia are attributed by them to the fact that the doses given (0·01 g. per kg. by subcutaneous injection) were 100 times less than those used by the earlier workers.

White cells

The total white cell count is according to the great majority of observers reduced after both injection and inhalation of benzole, sometimes to a remarkable extent. In Batchelor's experiments with inhalations of low concentrations (460–815 p.p.m.) the reduction was as much as from 73–92 per cent. In one of Engelhardt's animals (a rabbit, after 13 injections of 0·5 c.c. per kg.) the count reached the low level of 400. Weiskotten and co-workers (1920), using concentrations of benzole in air which they describe as similar to those found in industrial conditions (average amount vaporised per hour 26·6 c.c.) found that the lowest level reached (1,260) was never as low as that reached after subcutaneous injections.

An *initial leucocytosis* followed later by the characteristic leucopenia was described by the earlier workers (Selling, 1916; Langlois and Desbouis, 1907, etc.) but was not confirmed by Neumann

(1915). Later researches, however, appear to show that an initial leucocytosis may occur, but is not constant, and is to be attributed to an initial irritative effect on the haemopoietic system (Engelhardt, 1931). Schillowa (1933) found in all his animals a large increase of leucocytes during the first three months.

Diphasic leucopenia (i.e., a secondary fall in the leucocyte curve following a primary rise after exposure to benzole injections is discontinued) has been observed by Weiskotten and Steensland (1919) and by Batchelor (1927) in the case of subcutaneous injection. This phenomenon was not observed by Weiskotten and co-workers (1920) in the case of inhalation. A permanent lower level of leucocytes (average 6,166, as compared with 11,302 before exposure) was reached when the inhalations were discontinued and no further " deutero phase " was observed.

Relative lymphocytosis.—There have been differences of opinion as to whether a relative lymphocytosis is a characteristic feature. Batchelor, dividing the white cells into " polynuclear " (including polynuclear neutrophils, eosinophils and basophils) and " mononuclear " (including lymphocytes proper and large mononuclear forms) showed that there was a relative as well as an absolute decrease in the polynuclear forms and a relative increase in the mononuclear forms. This relative lymphocytosis had also been recorded by Selling, Fontana (1921) and others, and had been interpreted as an indication that the lymphocytes were more resistant to the toxic action of benzole than the leucocytes. Among those who have found no relative lymphocytosis are Neumann (1915), Muto (1931) and Nicolajew and Schparo (1929), the latter in fact stating that the lymphocytes are even more reduced than the leucocytes. Engelhardt's findings were variable, but on the whole a relative lymphocytosis was present in the majority of the animals. Sklawunos (1925), however, was able to produce a very marked leucopenia in animals without a corresponding diminution of lymphocytes, so that finally the white cell formation consisted almost entirely of lymphocytes. Lignac (1932) claims to have produced leukaemia and allied diseases in white mice by subcutaneous injections of benzole.

Degenerative changes in the white cells.—The degenerative changes in the white cells occurring in human benzole poisoning have also been observed in animals, but with similar differences of opinion in the hands of different workers. Thus, Woronow (1929) recorded destruction of leucocytes but no basophil granulation due to benzole itself, this phenomenon only occurring with its homologues; a finding which is contradicted by Engelhardt (1931).

Most workers, however, are agreed that the " shift to the left," indicating an immature polymorphonuclear response of the bone-marrow, is a characteristic feature in the blood of animals at some stage. (Hunt and Weiskotten, 1930; Wallbach, 1931; Engelhardt, 1931; Reznikoff and Fullerton, 1933, etc.) The findings of the latter in a cat injected with benzole may be given as typical of this response when it does occur :—

Day of Expt.	Leucocytes in thousands.	Immature polymorphs., per cent.	Mature polymorphs., per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.	Benzole subcutan. c.c.
1	39·0	30	21	45	2	2	0	2
2	44·4	73	18	6	3	0	0	2
3	20·2	60	18	12	8	2	0	2
4	25·2	60	13	16	7	4	0	2
5 cat dead								

Changes designated by Gloor (1929) as "nuclear pyknosis"—disappearance of normal segmentation, concentration of the chromatin, clumping of the individual parts of the nucleus, have been recorded by Beyer (1933) in rabbits; he states that it is uncertain whether these changes are identical with the "toxic granulation" described by Naegeli (1931), but that they indicate a toxic affection of the bone-marrow elements.

Eosinophils.—An increase of eosinophils, or rather "pseudo-eosinophils", has been described in animals, especially by Schmidtmann (1930) and Schillowa (1933). Beyer states that these constitute one of the differences in the normal blood picture of the human being and the rabbit; they are described as in the category of granulocytes, taking on Romanowsky-Giemsa stain with light-red large granules.

Red cells

Some anaemia appears to be the final result of benzole poisoning in animals, especially when injections are given, but this symptom is apparently not so prominent as in human beings. In inhalation experiments Engelhardt (1931) found the red cell count variable, sometimes remaining constant, at other times diminished or increased. In Batchelor's (1927) injection experiments the reduction in the red cell count (which ranged from 0 to 52 per cent.) occurred considerably later than that of the white cells; the red cells usually began to fall off and reached a minimum several days after the discontinuance of the injections, and remained low for some time afterwards. Silberberg (1928) and Orzechowski (1929) consider the variation in numbers and formation of red cells of much less importance than some of the white cell changes.

An initial increase, or hyperglobulia, in some of the experimental animals, was noted by the earlier workers, as well as by Batchelor and by Orzechowski (1929) and others. This has been attributed to a preliminary stimulation of the bone-marrow. A secondary increase, four or more weeks after the cessation of injections, was also observed by Batchelor. Anisocytosis and polychromatophilia were found in some cases, but normoblasts very rarely. Engelhardt (1931) observed normoblasts in only two cases. The appearance of reticulocytes, however, was a feature of the findings of Ferguson,

Harvey and Hamilton (1933). They seem to have made their appearance irregularly, in "showers", and these workers suggest that they may indicate the state of bone-marrow or haematopoietic activity in this form of anaemia as in many others. The same phenomenon observed by Paul, Friedlander and McCord (1927) is attributed by them to an irritant action of benzole on the haematopoietic tissues.

The haemoglobin level and colour index.—A reduction in the haemoglobin content, corresponding more or less to the reduction of red cells, appears to occur in animals. Thus Fontana (1921) noted reduction of haemoglobin to the extent of about one tenth, with a reduction of red cells to 3,000,000, as also did Secchi (1914) and Mauro (1925). Engelhardt (1931), with subcutaneous injections found a slow decrease of erythrocytes accompanied in most cases by no essential decrease in haemoglobin, and in one case by an increase, so that the colour index remained fairly high. In inhalation experiments the two factors varied more or less simultaneously.

Resistance of red cells.—In injection experiments Engelhardt (1931) found the resistance somewhat increased, but with inhalation the findings were not characteristic.

Sedimentation rate.—A slight increase in the sedimentation rate, but not until late in the course of the toxic action, was observed by Engelhardt.

Blood platelets

A marked fall in the number of platelets, preceded in some cases by a rise, has been noted by some observers, but it does not appear to be so characteristic in animals as in human beings. Duke (1913) found that large doses (5 c.c.) of benzole acted first as a stimulant then as a poison to the platelet-forming organs : the count first rose to 1,780,000 then fell rapidly to about 61,000. In small doses (2 c.c.) it acted only as a stimulant, causing a gradual rise in platelet count, which later fell, but not below the normal. Orzechowski found no change in the thrombocyte count, but Hultgren (1926) confirmed the findings of Duke, as also did Hurwitz and Drinker (1915). The reduction of platelets observed by the latter workers approximated to that recorded by Duke, though wide variations occurred, the average number following benzole injections in rabbits (average 2 c.c. per kg. body weight) being 233,800 (normal average 683,400). They were unable to reduce the count below 31,000, and the animals showed no haemorrhagic symptoms, such as occur after a more extreme lowering of the count. Where the platelets and leucocytes were much diminished in number the marrow usually showed well-marked aplasia, but destructive changes were rarely noted without accompanying signs of regeneration.

Hurwitz and Drinker (1915) were impressed by the fact that the blood platelets may remain at a high level at a time when the white cells have almost disappeared from the circulation. They suggest that this fact may be explained either by a very rapid regeneration

of the megakaryocytes of the bone-marrow (forerunners of the blood platelets) or a higher resistance of these elements to the toxicity of benzole than of the forerunners of the polymorphonuclear leucocytes and erythrocytes. Schillowa (1933) also found that the number of blood platelets corresponded with the number of megakaryocytes in the bone-marrow.

Factors of coagulation

Although it has been observed by Duke (1913) that the blood of animals poisoned by benzole *may* clot at the normal rate even when the platelets are reduced to 10 per cent. of the normal, it had also been shown that when the thrombocytes are at a very much reduced level the blood tends to show delayed coagulation, and the findings of the early observers, especially Santesson (1897) of symptoms of purpura haemorrhagica in clinical benzole intoxication gave special point to investigation of this aspect of benzole poisoning in animals.

The coagulation factors, prothrombin, antithrombin and fibrinogen, were investigated by Hurwitz and Drinker. It was found that injections of benzole produced a diminution of circulating prothrombin, but that the antithrombin and fibrinogen were little changed from the normal. The reduction in prothrombin is regarded as being due partially to the reduction of blood platelets, which contain prothrombin, but only partially. There was no parallelism between the extent of bone-marrow injury, the number of blood platelets and the relative amount of prothrombin in the blood; therefore it appears that either some other tissue or organ in addition to the bone-marrow is concerned in prothrombin formation or that a minimum amount of myeloid tissue suffices to keep the quantity of prothrombin above a dangerous level.

Immunity reactions

The more or less selective action of benzole on tissues and cells concerned in the production of antibodies and the defence against infection, offers an explanation of the results obtained by Rusk (1914), Schiff (1914), Simonds and Jones (1915), Hektoen (1916) and Wallbach (1933) with regard to the inhibiting influence exerted by benzole on the natural immunity reactions of the body.

Antibody formation.—Schiff (1914) found that in guinea-pigs small doses of benzole (0·01 c.c.) injected intraperitoneally before the injection of antigen increased the reactivity to the second dose of antigen, whereas larger doses (0·03 c.c.) decreased the reactivity. He attributed this effect to the action of benzole on the tissues which produce antibodies.

Rusk (1914) recorded that the injection of benzole either at the same time as or before the antigen greatly reduced the formation of lysin for sheep corpuscles and of precipitin for horse serum. Simonds and Jones (1915) also observed a reduction of lysin for dog corpuscles and of agglutinin and opsonin for typhoid bacilli. The

reduction of specific precipitin and lysin by benzole was fully confirmed by Hektoen (1916), and he stated that " the obvious explanation of the depression of antibody formation under benzene is damage to the marrow and the lymphatic structures which we have strong reasons to believe are concerned directly with this formation." While considering that the leucocytogenic centres are largely concerned with the elaboration of antibodies, however, Hektoen appears to agree with Simonds and Jones, who pointed out that these elements may not be exclusively affected, since benzole also attacks, directly or indirectly, the lymphocytes and the erythroblastic elements.

Phagocytosis.—A reduction in phagocytic activity of the leucocytes has been recorded by Hektoen and confirmed by Wallbach (1933). Hektoen (1916) found that in rabbits with benzene leucopenia the cytophagic index of the leucocytes for staphylococcus under the opsonic influence of normal rabbit serum fell to levels as low as 0·5 to 0·3 with leucocyte counts of about 1,800. (This finding is in contrast to experiments *in vitro*, where small amounts of benzene have been stated to promote phagocytosis (Hamburger, 1916).) Wallbach has studied the reaction of the organism to the injection of various bacteria, and finds that in severe benzole poisoning no cellular phenomena take place which point to repulsion or digestion of the bacteria injected. He states (1933) that the leucopenic action of benzole may be completely inhibited by the action of many bacteria.

Resistance of animals to infection.—It appears from the above experiments that benzole may lower the anti-infectious powers of the body in at least three ways :—

(*a*) by reduction of the number of leucocytes ;
(*b*) by reduction of antibodies ;
(*c*) by reduction of the phagocytic activity of leucocytes.

The actual lowering of resistance to infection has been shown in fact by several groups of observers. Lowered resistance to *pneumonia* was observed in rabbits by Winternitz and Hirschfelder (1913). Having induced leucopenia by means of injections of benzole they produced pneumonia by intratracheal insufflation of pneumococci, and found a marked lack of resistance to the infection, few leucocytes being present in the exudate. Further observations to the same effect were published by Kline and Winternitz (1913). Lowered resistance to *tuberculosis* was recorded by White and Gammon (1914) in rabbits inoculated with tubercle bacilli and given benzole by inhalation. Lowered resistance to *infection by the common bacteria of inflammation and to chemical irritants* was indicated by the experiments of Camp and Baumgartner (1915). They produced inflammation by the application of croton oil and of heat to the ear of rabbits, and also by intramuscular injection of an unsterilised solution of carmine. In the former experiments the benzolised animals were apparently unable to respond by a leucocytic exudate and in the latter the widespread entrance and growth of bacteria in the tissues indicated that they met with little or no resistance.

Effects on the Metabolism of Animals

A deleterious effect of benzole on the metabolism of animals seems to be indicated by the experiments of Underhill and Harris (1923). They found a sharp rise in the urinary elimination of both creatine and total nitrogen following subcutaneous injection of benzole into rabbits. If creatine may be regarded as an index of endogenous metabolism (Mendel and Rose, 1911) it would appear that benzole acts not only on the blood elements, but exerts a catabolic influence on body tissues as a whole.

Estimation of Benzole in Blood and in Tissues

The chief methods of estimating the amount of benzole in the blood and tissues of animals or human beings subjected to exposure to benzole vapour are described by Peronnet (1934).

(1) *Method of Lazarew and co-workers* (1931).—The benzole is extracted by a current of air flowing over a sample of blood, and the amount present in the air measured by the method described by Matmajew, Pronin and Frost (1930), which consists in combustion of the air in an electric oven and titration of the carbon dioxide formed by conductivity.

(2) *Method of Gadaskin* (1928).—The oxalated blood is nitrated by means of sulphuric and nitric acid and the *meta*dinitrobenzene formed is reduced to *meta*phenylenediamine, which by oxidation with dimethyl*para*phenylenediamine gives a violet colour.

(3) *Method of Peronnet* (1934).—The benzole extracted from a slightly heated sample of blood is nitrated to *meta*dinitrobenzene, which is then diluted with distilled water, neutralised and alkalinised. Alcohol is added, then a solution of laevulose in 70 per cent. alcohol and soda. The violet colour formed is compared in a colorimeter with that produced by a benzene solution of known concentration. This method is not applicable in the presence of xylene or toluene.

A modification of this method has been used by Koppenhöfer (1935) in estimating the benzole content of the blood and tissues in a fatal human case of benzole poisoning.

Absorption and Excretion of Benzole in Man

Absorption of benzole takes place chiefly by inhalation; owing to its lipoid-solvent action, absorption through the skin is possible, but is much less important than through the respiratory tract (Litzner, 1932). According to Lehmann *et al.* (1910) the proportion absorbed by inhalation may reach 80–84 per cent. of the vapour contained in the air.

Excretion of benzole also takes place chiefly through the lungs ($\frac{8}{10}$ by the lungs, scarcely $\frac{1}{10}$ by the urine, according to Feil, 1933). Benzole is not excreted as such in the urine, but is previously oxidised in the body to phenol, pyrocatechin or hydroquinone, and excreted in combination with sulphuric or glycuronic acid (Nencki and Giacosa, 1880; Schmiedeberg, 1881; Jost, 1932). A further portion, by oxidation of the benzene ring, is converted to muconic acid (Jaffé, 1909), but according to Jost (1932), this substance is not of great importance in chronic benzole poisoning, since it is only formed by rapid oxidation. Jost has examined these constituents in the urine of workers in the printing industry (exposed to benzole, xylole, and

toluole) and has found in the case of benzole a distinct increase in sulphuric and glycuronic acids and in phenol. His actual figures, and the normal figures given by Späth and Tollens (1909) respectively are as follows :—

	Normal daily average.	*Benzole poisoning, daily average.*
	g.	g.
Sulphuric acid	0·18	0·407
Glycuronic acid	0·62	1·08
Phenol		
(1) Volatile phenol (phenol and cresol)	0·03–0·07	0·17
(2) Non-volatile phenol (dioxybenzene) ..	0·015–0·05	0·07

These results may be correlated with the recent findings of Yant *et al.* (1936) which have already been described (p. 15). These workers state that normally the total sulphates in the urine consist of 85–95 per cent. of inorganic sulphates and 5–15 per cent. conjugated. After exposure to benzole it is believed that phenolic products of oxidation or metabolism of the benzole become available and the conjugation reaction is increased with a shift of the system inorganic sulphates $\rightleftharpoons$ conjugated sulphates to the right. This shift may proceed to the point of complete elimination of the inorganic sulphates. It is suggested by Yant *et al.* that the striking nature and reliability of the change in the sulphates in the urine of animals exposed to benzole should serve as a measure of the exposure and potentially harmful conditions in workers, before injury to the organism has occurred. It is not considered to be a method for proving exposure to benzole, because the extent to which other agents or physiological or pathological conditions may affect the sulphate response has not yet been determined (e.g., severe liver damage, as in carbon tetrachloride poisoning, would tend to retard the conjugation of sulphates in the liver and therefore decrease the sulphate response). It is emphasised that the changes are merely indicative of exposure and not of poisoning or damage, but they are a definite enough indication of benzole exposure for removal of the individual and investigation into the cause.

Acute Toxic Effects in Man

In the earlier literature, cases were reported with some frequency of acute, sometimes fatal, poisoning from swallowing benzole. Such were for example the two cases recorded in St. George's Hospital Reports for 1877–78, and those of Averill (1889), Simonin (1903), (in the latter case the patient survived but developed swelling and oedema of the skin), Hetzer (1922) (in which the poisoning was followed by intense toxic gastritis and later pyloric stenosis), and Nick (1922) (in which cure followed the injection of 5 c.c. of a 10 per cent. lecithin emulsion.)

Even before the war cases of acute poisoning from inhalation of fumes of benzole were not infrequent—Rambousek in 1911 reported twenty-two cases, 18 of which proved fatal—and generally occurred, as have the more recent cases, from the sudden inhalation of large quantities of benzole vapour in connection with coal tar stills and benzole tanks. In practically all the fatal cases which have been reported to the Home Office since 1908—15 in all—death has followed the entry of the workman into a tank or still containing benzole or having contained it at some time.

With regard to the possibility of reducing the incidence of acute benzole poisoning from this cause, Mariam-Wolfen (1925) suggests certain measures for the cleaning of benzole containers. He states that removal of benzole residues from tanks is not possible by means of water alone, that in fact such a method increases the danger, since the benzole, being of comparatively low specific gravity and scarcely soluble in water, forms a layer on the walls of the vessel which is later vaporised. The passage of steam through the container, however, with the provision of several openings for the escape of the steam and volatilised benzole, and of an exit at the lowest level of the container for the escape of the benzole-containing water of condensation will, he claims, constitute an entirely successful procedure for cleaning out vessels containing benzole and removing the residue; this method should, if carried out universally, much reduce the danger of severe and fatal cases of benzole poisoning.

Factors Predisposing to Acute Benzole Poisoning

The histories of the fatal cases, as described in the reports of the Benzole Poisoning Committee of the National Safety Council (1922), of McCord *et al.* (1932) and of Hamilton (1925), show great variation in individual susceptibility. Sometimes a man exposed for a short period died, while another exposed for longer and more intensely survived.

Physical exertion was often associated with a fatal termination. In many instances members of a rescue party were fatally poisoned while the original victims, after a period of unconsciousness, survived. Such were the cases reported by Lewin (1907), by Hamilton (1925), etc., and they led to the belief that muscular exertion tends to increase the susceptibility to poisoning and to decrease correspondingly the prospects for recovery in acute cases.

Emotional reaction has also been shown to be a factor in increasing the severity of the intoxication. In a case quoted by Feil (1933) for example, the victim rushed suddenly out of the space where he had been working, cried out that he was burning, and dropped dead, while a very interesting account of a "Massenvergiftung" by benzole in a Russian factory was described by Dvoretsky (1914) where the medical authorities considered that of the 230 persons involved, the greater number were affected by hysteria only, and that a few suffered from benzole poisoning together with hysteria.

The interesting results of the experiments carried out by Nahum and Hoff (1934) on the mechanism of sudden death in animals intoxicated with benzole appear to shed much light on this question of individual susceptibility in human beings. They point out that in muscular exercise there is a reflex cardio-acceleration, with a liberation of sympathin, while in excitement there is also a well marked liberation of adrenaline into the blood stream. Their experiments on animals showed that benzole effects the liberation of adrenaline and sensitises the myocardium to its action. The adrenaline and sympathin contribute to the production of ventricular extra-systoles and the amount liberated determines the severity of the attack. Thus the danger of death from ventricular fibrillation is increased by either muscular exertion or emotional excitement, or both, and Nahum and Hoff consider that many of the individual variations in susceptibility reported in the literature may be due largely to variations in the adrenaline response.

Symptoms of Acute Poisoning

The gravity of the symptoms of acute benzole poisoning is in general in accord with the amount absorbed and the length of exposure. In the cases reported to the Home Office since 1921 the fatal cases were exposed for periods varying from 45 minutes to 3 hours to concentrations which must have been very high, since practically all of them took place in closed spaces containing the vapour evaporating from residues of benzole.

Feil (1933) describes several forms of acute benzole poisoning.

(*a*) *Mild form*—characterised by a state of euphoria followed, if the subject is not removed from exposure, by giddiness, headache, nausea, vomiting, staggering gait, sensation of tightness in the chest, and inability to escape from the site of poisoning. Of the 20 non-fatal cases reported to the Home Office since 1921, 12 might be regarded as in this class, 8 being rendered partially unconscious, while 4 complained only of dizziness, headache or nausea.

(*b*) *Severe form*, in which after inhalation of large amounts of the vapour, the principal symptoms are related to the central nervous system—convulsive movements, paralysis, unconsciousness with dilated and non-reacting pupils, followed in the most severe cases by death. Of the 28 cases reported to the Home Office from 1921 to 1935, 8 were fatal and 8 others rendered completely unconscious. According to Fischer (1932) this form of intoxication is not unlike that produced by other fat-soluble narcotics; he notes specially that there is no blue-gray colour of the face as in poisoning by nitrobenzene, though Hamilton observed cyanosis of mucous membranes and finger tips in some of her cases.

(*c*) *Typical forms* in which intoxication is ushered in either by coma or by a state of violent excitement and delirium. Such is the case described by Feil himself, and a case reported by Harrington (1917), where the man is described as having "acted crazy", becoming wildly excited and later unconscious.

After-Effects in Non-Fatal Cases

In the majority of patients who recover from acute intoxication there are no immediate after-effects, except temporary symptoms such as pain in the head and chest, shortness of breath, giddiness, loss of appetite and sometimes nausea and even vomiting. Late manifestations and sequelae have however been recorded. The most severe case is perhaps that recorded in the Report of the Chief Inspector of Factories and Workshops for 1918, where a man two nights after his return to work relapsed into unconsciousness from which he never recovered.

The following are the chief sequelae of acute poisoning recorded:—

(*a*) Dizziness and uncertain gait lasting about 12 days, as in the cases reported by Gerhard (1910) and Wyss (1910).

(*b*) Respiratory catarrh and pleurisy (Gerhard, 1910 ; Schaefer, 1909 ; Kobert, 1906).

(*c*) Nervous disorders—depression, insomnia, bad dreams (Wyss, 1910), nervous exhaustion (Lewin, 1907).

(*d*) Skin changes—a residual yellow pallor was observed in one of Lewin's cases ; and an exanthem over the back by Gerhard.

(*e*) Cardiac distress. Spells of cardiac distress lasting four weeks after recovery were reported by Cronin (1924), and by Lewin, the latter also observing a blowing murmur.

Post-Mortem Findings

The earliest record of an autopsy on a case of acute benzole poisoning is that of Sury-Bienz (1888), in which the chief findings were bright red spots on the body and a dark red, fluid condition of the blood, which remained fluid for a long time after death.

The chief results of post-mortem examinations since that time, including the very complete and detailed examination of a case made recently by Koppenhöfer (1935) may be summarised as follows :—

(1) *Petechial haemorrhages.*—The findings of Sury-Bienz in this respect were confirmed by Beinhauer (1896). Minute haemorrhages in the pleural, gastric and intestinal mucosa were also noted by these two workers in the pancreas ; by Buchmann (1911) in the brain and pericardium ; in the lungs by Heffter (1915), Binder (1921), and Ziel (1925) ; in the subcutaneous fatty tissue and serous membranes by Floret (1926) ; in the brain, pleura, gastro-intestinal mucous membrane, kidney, pelvis, ureter and bladder by Koppenhöfer.

(2) *Fluidity of the blood.*—The observations of a dark or cherry red, fluid condition of the blood by the earlier workers was confirmed by Binder (1921), Heffter (1915) and Floret (1926). Heffter remarked that in spite of the blood remaining fluid for a long time after death, there was no evidence of haemolysis. The result of a test for methaemoglobin in the blood made in a case reported by Martland (quoted by Hamilton, 1931), was negative, but Carter (1928) stated that the spectroscopic appearances of the fluid blood in a fatal case were those of oxyhaemoglobin and that reduction was easily effected by ammonium sulphide. Koppenhöfer (1935) also demonstrated the presence of oxy- but not of methaemoglobin.

(3) *Congestion or cyanosis of the internal organs.*—Floret (1926) describes the phenomenon as " all the organs being full of blood," as also does Ziel (1925). Cyanosis of the liver, spleen and kidneys in one case and of the brain in another was observed by Martland in 1917, and in another case

(cited by Hamilton, 1931) fluid blood in the right side of the heart with marked distension. Koppenhöfer (1935) observed hyperaemia of all the internal organs and an albuminous fluid exudate in the liver and lungs.

(4) *Changes in the respiratory organs.*—Small areas of interstitial emphysema in the lungs, reddened and irritated bronchi (Martland, 1917), oedema of the lungs (Binder, 1921; Koppenhöfer, 1935) and "bloody mucus" in the air-passages (Heffter, 1915; Sury-Bienz, 1888) are among the findings reported, while in a case reported to the Home Office in 1927, the lungs showed recent adhesions and cyanosis. In this case traces of pyridine (0·5 per cent.) were present in the vapour to which the man, a worker in a dye factory, was exposed.

(5) *Benzole in the internal organs.*—There has been some difference of opinion until recently as to whether benzole can be detected, either by the odour, or by chemical analysis, in the organs after death. Martland (1917), for example, noted a distinct odour on section of the lungs, while in the Home Office case mentioned above the trachea, larynx and liver smelt of benzole. In another case examined by Martland, however (quoted by Hamilton, 1931), there was no distinctive odour in the lung cavity or in the brain, though the autopsy was made while the body was still warm. In Koppenhöfer's (1935) case, the post-mortem was made 24 hours after death, and he states that a strong typical aromatic odour issued not only from the muscles as they were cut and from the body cavity, but even more decidedly from the brain and spinal cord.

With regard to the actual estimation of benzene in the tissues, Koppenhöfer, in spite of the statements of Heffter (1915), Beinhauer and Buchmann, etc., that benzene could not be detected chemically in the bodies of subjects dying from acute poisoning, has been able to estimate its presence not only qualitatively but quantitatively. He used a modification of the method described by Peronnet (1934) (see p. 30), obtaining needle-shaped crystals of dinitrobenzene and producing the intense violet colouration by adding a 1 per cent. solution of laevulose to an alkaline alcoholic solution of these. In contrast to the opinion of Heffter (1915) and of Joachimoglu (1915) that the greatest amount of benzole should be present in the brain, and that this should denote a special affinity of benzole for the lipoid tissue of the brain and spinal cord, Koppenhöfer found the highest percentage of benzole in the blood. He calculated that the whole blood of the body of this man weighing 72 kg. would contain approximately 1 c.c. of benzole. He believes that in the most severe cases of benzole poisoning, at any rate, the essential lesion is a colloid-chemical disturbance of the blood rather than a disturbance of the lipoidal tissue of the central nervous system.

The following are Koppenhöfer's figures for the percentage amounts of benzole in the different organs:—

Organ.	*Benzole mg. per 100 g.*
Blood	14·0
Spinal cord	12·6
R. kidney	10·3
Spleen	9·4
Brain	7·5
R. lung	5·5
Liver	5·3

(6) *Changes in the urine.*—No benzole was detected in the urine taken from the bladder after death by Heffter or by Martland, but both as well as Beisele (1912) and Simonin (1903) found an increased amount of "phenol bodies" (phenol-sulphonic acid in Heffter's case). Heffter states that in cases which are rapidly fatal, phenol bodies are not usually found, since the change to conjugated acids is fairly slow. Urobilin, diminished urea and diminished chlorides were observed by Simonin (in a case of poisoning by accidental ingestion of benzole). No blood, albumin or haematoporphyrin were detected by Beisele.

Treatment of Acute Benzole Poisoning

The usual measures are artificial respiration, administration of oxygen, etc., but intravenous injections of lecithin have been claimed by Nick (1922) to have saved life in one case.

Chronic Benzole Poisoning in Man

While animal experiments have undoubtedly elucidated some of the problems of benzole poisoning in human beings, their results cannot be said to be applicable in all respects to human intoxication. The variation of individual and species susceptibility, and the liability to infection of animals injected with benzole are only two of the factors which make the complete picture of benzole intoxication unlike that found in human beings. Among the facts which have emerged from the more recent researches on the subject perhaps the most outstanding is the variability in the clinical syndrome and blood picture hitherto regarded as typical. Thus Hamilton quotes a case where with the typical symptoms of bleeding from the gums and nose, retinal haemorrhage and purpura haemorrhagica, the only abnormal feature of the blood picture was the absence of blood platelets. In the blood picture itself very striking variations from the " typical " picture of leucopenia with neutropenia, thrombopenia and anaemia have recently been reported by Continental workers—e.g., Biermer's anaemia, without haemorrhages (Weil, 1933) splenomegaly and myeloid leukaemia (Weil, 1932) and typical acute leukaemia (Deloré and Bergomano, 1928).

The Clinical Syndrome of Chronic Benzole Poisoning

(*a*) *The most commonly observed form*

In the most commonly observed form the development of a syndrome pointing to damage of the blood-forming organs is preceded by slight preliminary symptoms—headache, giddiness, drowsiness, lassitude, loss of appetite, nausea, even vomiting. Sometimes more definite symptoms appear at this stage—pallor, anaemic condition, metrorrhagia or menorrhagia in women, ecchymoses. Robert-Lèvy (1935) states that at this stage an examination of the blood would show leucopenia and neutropenia. Generally it is the occurrence of haemorrhages which reveal the condition as one of benzole poisoning—epistaxis, bleeding from the gums, persistent and heavy metrorrhagia, subconjunctival and retinal haemorrhages, ecchymoses and a purpuric eruption. Haemoptysis or even haematemesis may occur ; in a case reported to the Home Office in 1929 the other symptoms were comparatively slight (lassitude and oppression in the chest) and the changes in the blood picture not of great severity (leucocyte count 4,800, with neutrophils 50 per cent. and lymphocytes 39 per cent.) but were preceded by haematemesis. Ulcerations of the buccal and tonsillar mucosa, scorbutic in appearance, are not uncommon, though according to Pulford (1931) they never progress to the gangrenous and sloughing condition found sometimes in agranulocytosis.

The patient appears characteristically pale, dyspnoeic, anxious, has a rapid pulse and often a raised temperature.

The frequency of symptoms ordinarily complained of among women suffering from the effects of benzole poisoning was found by A. Ross Smith (1928) to be as follows :—

Complaint.	No.	Percentage.
Headache	18	60·0
Excessive fatigue	14	46·7
Dizziness	13	43·3
Nausea	10	33·3
Anorexia	9	30·0
Weakness	8	26·7
Nervousness	6	20·0
Numbness and tingling	5	16·6
Frequent urination	4	13·3
Nose bleeding	4	13·3
Disturbed sleep	4	13·3
Indigestion	4	13·3
Frequent menstruation	3	10·0
Shortness of breath	2	6·7
Skin eruptions	2	6·7
Vomiting	2	6·7
Pain in abdomen	2	6·7

Neurological symptoms. Ross Smith (1928) considers the symptoms related to the nervous system found in a number of the women examined evidence of the neurotoxic action of benzole. Similar evidence was provided in a case reported by Fauré-Beaulieu and Lévy Bruhl (1922), also in a woman. The nervous symptoms in this case took the form of increased tendon reflexes, bilateral clonus, positive Babinsky, impairment of deep sensitivity, pseudo-tabetic lesions with paraesthesias, ataxia and paraplegia and motor impairment—signs indicating lesions of the posterior columns and pyramidal tracts. Such lesions, according to the National Safety Council Report, were probably the combined effects of the prolonged and persistent anaemia, and of the possible direct action of the benzole on the central nervous structure, inasmuch as it has been found that benzole finds special lodgement to excess in these tissues.

Neuritis of the median nerve has been observed by Landé and Kalinowsky (1928) and retrobulbar neuritis, with dimness of vision and headache by Goldmann (1930) in a worker in spray lacquering.

Epilepsy has also been related directly to benzole poisoning by Korvin (1933). She quotes the case of a female worker exposed to benzole who developed typical epileptic attacks after some months. No other clinical symptoms of benzole poisoning, except lassitude and loss of appetite were present, but Korvin states that the diagnosis was strongly supported by the presence of a typical blood picture—a leucopenia of 2,000 and a relative lymphocytosis of

50 per cent. Korvin mentions a rather similar case reported by Albrecht in 1932, which was at first diagnosed as a brain tumour, but in which the diagnosis of benzole poisoning was made more probable by the favourable progress after removal from exposure.

Localised myelitis has also been observed by Sänger (1914) in a benzole worker. Spastic paresis, nystagmus and a positive Babinsky reflex were present and recovery took place on removal from exposure.

Frequency of urination was mentioned by Starr (1922) as a common symptom among the milliners whom he examined and, was attributed by him to the possible excretion of phenols in the urine. This symptom was also observed by Ross Smith (1928) as a transient phenomenon.

(*b*) *A more severe form*

In the more acute form, many cases of which prove fatal in spite of removal from exposure to benzole, the picture is that of a progressive severe anaemia, ushered in by *purpuric manifestations*; death occurs from a few days to 1 or 2 weeks after the appearance of the purpuric symptoms. This was the type of case which first drew attention to the existence of benzole poisoning in industry, as in the famous cases of Santesson (1897) and in those reported by Lenoir and Claude (1897), Selling (1916), Hogan and Schrader (1923), Legge (1919–20—the first cases reported in Great Britain), Harrington (1917), Flandin and Roberti (1922), and many others. It was the typical syndrome in a series of cases reported by de Balsac, Heim and Agasse Lafont (1933), in workers using an adhesive where benzole was the solvent. Forty cases were affected, 8 being fatal, and 36 showing purpuric manifestations—eruption, haemorrhage from the gums and nose, ecchymoses, and metrorrhagia. A feature of this outbreak was the delay in the onset of the purpuric symptoms, which appeared some days after the initial slight symptoms of headache, giddiness, digestive troubles, anorexia and asthenia.

Cause of the purpuric manifestations.—Although variations in the condition of the blood itself (thrombopenia, anaemia) are regarded as having some influence on the tendency to haemorrhage in benzole intoxication, they are apparently not the whole cause (Litzner, 1932). Mitnik and Genkin (1931) have in fact observed no haemorrhage in the presence of severe thrombopenia, and, conversely, haemorrhage in the presence of a normal blood platelet count; they also found no diminution in the fibrinogen and thrombin content of the blood. Injury to the capillary vessels has been put forward as an important factor in the cause of the haemorrhage by Santesson (1897), Landé and Kalinowsky (1928) and Mitnik and Genkin (1931). Santesson related this injury to fatty degeneration of the capillary endothelium, and Mitnik and Genkin postulate a preliminary functional disturbance, in the sense of a strong vasomotor spasm with long continued stasis. Litzner (1932) also states that the Rumpel-Leeds sign

(production of capillary haemorrhage by means of stasis) is an early symptom of benzole poisoning, and that this phenomenon, together with a lengthening of the time of bleeding in the presence of a normal coagulation time constitute further evidence of capillary injury.

Terminal infection is often the cause of death in cases of great severity (owing, it is believed, to decrease in the leucocytic defences, as shown in the case of animals). Gangrenous periostitis and osteomyelitis were observed in a fatal case by Löwy (1926), necrosis of the jaw by Hegler (1928) and severe haemorrhagic ulcerative gingivitis by Laignel-Lavastin *et al.* (1928). This feature was also shown in two fatal cases recently (1934) reported to the Home Office. In the first subject, a leather sprayer, the anaemia was so severe as to arouse suspicions of pernicious anaemia, and at autopsy there was found a terminal sepsis of the tonsil and lower end of the oesophagus. In the second, a female worker in leather cloth and lacquers, death was due to aplastic anaemia with septicaemia, the latter arising from a septic endometritis.

(*c*) *Slighter forms*

Cases of less severity, with slight symptoms, and no very great disturbance of the blood picture may recover under treatment and with removal from exposure. Such were the cases reported by Teleky and Weiner (1924) occurring in the manufacture of rubber goods. The symptoms were variable, headaches, nausea, eructation, vomiting, tendency to bleed from membranes, irritation of conjunctivae and menstrual irregularities and anaemia with reduced platelets and inversion of the leucocyte-lymphocyte formula. Substitution of benzine for benzole resulted in definite improvement both of the symptoms and of the blood picture.

(*d*) *Latent form*

Falconer (1931) quotes a case where after 15 years' exposure the only demonstrable sign of benzole poisoning was a reduction of blood platelets (to 100,000 per c.mm.). The patient was removed from exposure and two years later developed an acute respiratory infection, followed by the full-blown picture of benzole poisoning, which proved fatal. Falconer states that an infection such as influenza may precipitate frank benzole poisoning with leucopenia, anaemia, purpura, and haemorrhages several months after exposure. Cases of progress of the disease without further exposure have also been reported by Santesson (4 of his cases developed symptoms only after they had left the factory) and by Rohner and co-workers (1926). In one of the cases reported by the latter authors, eye irritation was the only symptom during exposure, but haemorrhage and a fatal aplastic anaemia developed a month later.

Duration of Symptoms after Removal from Exposure

From the observations of Gounelles and Dumas (1935) it appears that benzole intoxication produces a lasting effect on the organism, manifested both by symptoms existing for long periods after removal

from exposure and by the persistence of an abnormal blood picture. Examination of 4 women, 16 to 18 months after purpuric manifestation and typical blood changes had led to their removal from exposure (Dumas, 1934; Israel, 1934) showed that they were still suffering from asthenia, fatigue, pallor, slight attacks of purpura, gingivitis with loss of teeth, and in two cases metrorrhagia and menorrhagia. Gounelles and Dumas (1935) remark that the metrorrhagia prolongs the injurious effect of the benzole and tends to produce a chronic hypochromic anaemia, which they have found resistant to iron therapy, except in so far as it produces a purely palliative result.

Skin Changes

Although a chronic toxic effect of benzole on the skin, of an eczematous nature, has been described by Landé and Kalinowsky (1928) and Oppenheim (1930), these are regarded by most workers, when they occur, as probably allergic in nature (innate or acquired susceptibility according to Engelhardt (1933)). Landé and Oppenheim have described them as characterised by folliculitis, cornification of the seborrhoeic glands, hyperkeratosis and hyperpigmentation, and have regarded them as arising from the fat-solvent action of benzole on the superficial layers of the skin, leading to irritation and inflammation of the deeper layers. No such changes were observed by Dimmel (1933) in any of the 66 cases of benzole poisoning recorded by him.

Factors Concerned in Chronic Benzole Poisoning

Sex, age and pregnancy.—It has been rather generally believed that young subjects, especially women, are specially liable to chronic benzole intoxication (Feil, 1933; Pulford, 1931; Meda, 1922; and others). Whether women are actually more susceptible than men appears, however, to be uncertain, since groups of opposite sexes working under exactly similar conditions do not seem to have been investigated. In Dimmel's investigation both men and women were affected, and though the conditions of work in this rubber factory were such that it was impossible to say definitely that both sexes were equally exposed, Dimmel found no grounds for believing that women showed more susceptibility than men.

That women may suffer more from subjective symptoms than men having an equal degree of leucopenia however is suggested by records secured by Ross Smith (1928) in one factory (a camera manufacturing plant) where among a group of 33 women only 6 made no complaint of symptoms such as headache, dizziness, nervousness, weakness and great fatigue, and where 11 positive and 1 suspected case of benzole poisoning were found. Of 15 men exposed under the same conditions, whose white cell counts were below 5,625, only one had symptoms associated with the work.

An increased susceptibility in pregnant women has been definitely observed (Meda, 1922; Hamilton, 1925; Ross Smith, 1928). The latter author quotes a case in which no symptoms appeared until

the woman became pregnant ; she then suffered from severe nausea, vomiting, bleeding from the nose, gums and rectum and into the skin. After the birth of a premature child she had a severe uterine haemorrhage and died. According to Feil (1933) pregnancy should constitute an absolute contra-indication to benzole exposure.

Youth, in women especially, was stated in the Report of the National Safety Council (1926) to be a predisposing factor, but this was not found to be the case by the New York Department of Labour, 1927. The percentage of positive cases was lowest in the youngest group and highest in the oldest. Ross Smith remarks that the opinion of earlier workers in this respect may have been due to the extreme youth of the women exposed in their studies. In the factory from which Selling's cases came for instance, all the 14 girls exposed were between 14 and 16 years of age, whereas in the factories studied in the Department of Labour Report the average age was 28.

Length of exposure.—The findings of the Department of Labour seem to indicate that where susceptibility to poisoning exists it tends to develop during the first year, the percentage of positive cases being lowest in the group with an exposure of 3 months or less but showing little difference in groups with an exposure of 3–12 months, 1–4 years, and 4 years and over respectively. According to Robert-Lèvy (1935) a latent period may extend from 3 weeks to 6 months or even up to 3, 6, or 12 years. Among the cases reported to the Home Office since 1926, the time of exposure seems to have had little relation to the severity of the intoxication. Three cases exposed for 18 months, 2 years and 4½ years respectively were comparatively little affected, while 2 cases of 4 months and 31 years exposure respectively both proved fatal. Feil (1933) emphasises the fact that long-continued exposure may result in a progressive hypersensitivity.

Intensity of exposure.—The actual amounts of benzole in the air of factories in which cases of benzole poisoning have been reported have already been discussed. In the fatal cases reported by Legge in 1918 the average amount was 550 p.p.m. It is interesting to observe that in the factory in which one of the deaths occurred, that of a man employed for 6 months in coating the metal rims of tyres with a benzole solution of rubber, the ventilation had been diminished during the last 2 months by the carrying out of structural alterations. The Report of the National Safety Council (1927) states that benzole poisoning occurs with greater frequency in cold weather when natural ventilation is usually reduced to a minimum by closed windows and doors so that the concentration in the atmosphere reaches a maximum. Atmospheric conditions of temperature and humidity also play an important part. At times of heat and high humidity, other things being equal, spontaneous and sporadic outbreaks are most apt to appear.

According to Robert-Lèvy (1935) and Merklen and Israel (1934) the intensity of exposure determines to some degree the type of

blood picture. The latter workers state that the "classical aleukaemia" is only produced with long exposure and lack of individual resistance, while short and moderate exposure produces the "formes frustes."

Individual predisposition.—This according to Robert-Lèvy, is the most important factor in determining whether a given time and intensity of exposure will produce symptoms of poisoning among a group of individuals. Emile Weil (1935) has gone so far as to call it the "sol hématique"—an innate constitution of the haemopoietic tissues predisposing to their injury.

An apparent family susceptibility has been noted by Reifschneider (1922). He found three cases in one family; two of these proved fatal, the third patient a secondary anaemia and was removed before other symptoms developed.

Conditions of ill-health.—General lowering of vitality, respiratory diseases, especially tuberculosis, alcoholism (by virtue of its effect on the liver and brain), heart disease, nervous disorders, nephritis (by reducing the elimination of toxins) and obesity, are among the predisposing factors listed by the National Safety Council and by Feil (1933).

The Blood Picture in Chronic Benzole Poisoning

While the most characteristic blood picture in benzole poisoning remains that described by the earlier workers, a leucopenia with neutropenia, thrombopenia and some anaemia, it becomes increasingly evident that many cases present wide variations on this picture. Recently Emile Weil (1933–35) and Deloré and Bergomano (1928) have described such forms as a hyperchromic anæmia, similar to pernicious anaemia, and myeloid leukaemia with splenomegaly, and typical acute leukaemia. There appears to be the greatest difference of opinion on the question of the red cell variations. Hamilton (1934), for example, states that in human beings the destruction of red corpuscles is often more conspicuous than that of the white cells and states that out of 77 counts collected from the literature 17 showed leucopenia in excess of anaemia, and 22 anaemia in excess of leucopenia. Robert-Lèvy (1935) on the other hand states that benzole strikes first and electively the granular leucopoiesis and thrombopoiesis, and that the anaemia is less constant, develops later and is sometimes secondary to the haemorrhage. Some reconcilement of these various opinions may perhaps be gained from a statement in a recent textbook on haematology (Whitbey and Britton, "Disorders of the Blood", 1935). Here it is stated that "benzole may attack any or all of the (haematopoietic) tissues, usually the leucoblastic and thromboblastic tissues first and erythroblastic tissues last." Selling (1916) records 3 cases of benzole poisoning of which two showed thrombopenia followed by complete, aplastic anaemia, and one showed mild purpura without changes in the leucocytes and red cells. Larrabee (1924) records a case in which the tissues were affected in the order, leucocytic, thrombocytic

and erythrocytic, whilst Bamforth and Elkington (1931) describe 2 cases in which the order was, thrombocytes, leucocytes, red cells (these cases, however, were of poisoning from arsenobenzol).

The white blood cells

The total leucocyte count.—The typical effect of benzole poisoning is a reduction of white cells, sometimes to a very low level. The lowest recorded appears to be 104 (Hogan and Schrader, 1923). In one of Selling's cases the total leucocyte count was 480, in Harrington's 500, and in Laignel-Lavastine's 600, while values from 1,000 to 2,000 are very frequently reported. It is stated by some authors (e.g., Robert-Lèvy, 1935) that this reduction in white cells may go on to a complete agranulocytosis, indistinguishable from true agranulocytic anaemia except by the history of exposure to benzole. In this connection the work of Kracke and Parker (1934) on the effect of drugs containing the benzene ring is of interest. They state that such drugs, especially amidopyrin, may produce true agranulocytic anaemia. Merklen and Israel (1934) point out that in man, as also in animals (see Reznikoff and Fullerton), while hypogranulocytosis may result from the destruction of leucocytes by benzole, a liberation of immature granulocytic forms (myeloblasts, myelocytes) may be simultaneously provoked.

So great was the leucopenia in the cases of benzole poisoning recorded by the earlier workers that in 1912 Koranyi suggested taking advantage of this leucopenic action of benzole by using it as a therapeutic agent in leukaemia. Favourable results from this treatment were reported by several workers, including Kiralyfi (1913), Billings (1913), Barker and Gibbes (1913) and others, but its dangers were pointed out by Pappenheim (1913) and Klemperer and Hirschfeld (1913); very variable results were reported in the hands of other workers such as Myers and Jenkins (1913), etc. Thus, of late years, according to the Report of the National Safety Council (1926) " benzole therapy has more or less fallen into disrepute, due to lack of uniformity of action and the more or less transient nature of the results obtained." In view of the leukaemic effect of benzole reported by Emile Weil (1933) (see below) the variability in the results of its administration is not surprising.

Leucocytosis has been reported by a few workers both as an initial phenomenon and as a consequence of intercurrent infection. Rabe and Hirschland (1920) observed an initial increase of leucocytes after administration of minute doses to men and women while Löwy (1926) recorded an increase up to 16,000 in slight, fairly acute cases of poisoning. The presence of suppuration may also produce an increase of polymorphonuclear leucocytes (Paul, Friedlander and McCord, 1927; Meda, 1922).

Leukaemia on the other hand has been reported by Deloré and Bergomano (1928) and Emile Weil (1933). The latter describes two forms:—(*a*) Acute—as in Deloré and Bergomano's case, where a man, a worker in a pyramidon factory, died within three weeks of

the appearance of multiple enlarged glands, slightly enlarged spleen, anaemia with haemorrhages into the skin and mucous membranes, and gangrene of the palate. The white cells numbered 542,000, and myelocytes were present. (*b*) Chronic—as in a case reported by Emile Weil (1932), where a woman worker in a rubber factory, died after two years of myelogenous leukaemia, with typical post-mortem findings. The white cell count in this case was 68,000.

The differential count.—A relative lymphocytosis is found in most cases of benzole poisoning, the neutrophils being decreased in comparison with the lymphocytes. Instead of the normal ratio of 65–70 per cent. polymorphonuclears to 20–30 per cent. lymphocytes, values of 50–60 per cent. polymorphonuclears and 40–50 per cent. lymphocytes have been frequently recorded. In one fatal case reported to the Home Office in 1931 this ratio showed an extreme variation, viz., polymorphonuclears, 0·75 per cent.; lymphocytes, 96·25 per cent., while in another (1934) the values were 12 per cent. and 88 per cent. respectively. A relative *monocytosis* has also been recorded, notably by Laignel-Lavastine (monocytes, 51 per cent.) and Brindeau (1931). An increase in *basophil* leucocytes was recorded by Ross Smith (1928). *Myelocytes* have also been observed by Ross Smith, Merklen and Israel, Dimmel, etc.

Immature leucocytes.—An Arneth shift to the right is usually regarded as characteristic of chronic benzole poisoning, but in a case recorded by Mitnik and Genkin (1931) a shift to the left was observed with 22 per cent. of rod cells, 27 per cent. segmented cells and 34 per cent. lymphocytes.

Eosinophilia.—An increase in eosinophils has been recorded by some workers; de Balsac, Heim and Agasse Lafont (1933) 4–8 per cent.; Meyer (1931) up to 10 times the normal in 17 cases. In the series of cases in a rubber factory investigated by Dimmel (1932–33), eosinophilia was a characteristic feature, in one case rising to 53 per cent. Dimmel regards eosinophilia as a favourable prognostic symptom. Other workers, including Teleky and Weiner (1924) have entirely failed to observe any eosinophilia.

The red cells

As a rule a reduction of red cells occurs during benzole poisoning, leading to a moderate degree of anaemia, but in certain cases anaemia of great severity is the outstanding symptom. Emile Weil (1933) describes two forms of benzole anaemia:—(*a*) slight—as described by Delarue (1919) and Chambovet (1921), with pallor of mucous membranes, fatigue, anorexia, dyspnoea on effort, menorrhagia and metrorrhagia in women. (*b*) Severe hyperchromic—of the "pernicious" type—with a red cell count down to 1,860,000, and a colour index of 1·6. Similar cases have been described by Brindeau (1931), Rivet and Géréde (1928) and in some of the cases (fatal) recently reported to the Home Office (1934).

The total red cell count.—One of the lowest red cell counts recorded is that of a case of Brocher (1929)—630,000—while other very low

values are 880,000 (Hogan and Schrader, 1923), 900,000 (Hayhurst and Neiswander (1931) and 1,000,000 (Hamilton, 1925; Landé and Kalinowsky, 1928). The majority of cases, however, appear to range between 2 and 4 million per c.mm.

Abnormalities of the red cells.—Degenerative changes, including anisocytosis, poikilocytosis (Rohner and co-workers, 1926; Schneider, 1930; Hayhurst and Neiswander, 1931, etc), stippling, punctate basophilia and even the appearance of nucleated red cells have been reported with some frequency (Hunter and Hauflig, 1927; Ronchetti, 1922; Oettinger, 1919; Brindeau, 1931).

Resistance of red cells.—According to Schneider (1930) the resistance of the red cells in benzole poisoning is never decreased and is sometimes slightly increased.

Reticulated cells.—A slight reticulocytosis is recorded by Mitnik and Genkin (1931), also by Pulford (1931).

Haemoglobin level and colour index.—In most cases the haemoglobin level sinks concurrently with the red cell count so that the colour index is below 1, but in the severe cases, such as those described by Emile Weil, etc., the haemoglobin remains relatively high and a colour index of above 1 results. In two of the fatal cases reported to the Home Office in 1934, the colour indices were 1 and 1·06 respectively. Dimmel (1932) found a high colour index to be a feature of the severe cases recorded in his investigation, lying between 1·1 and 1·3 and falling below 1 with improvement in the condition. Hamilton (1934) states that out of 75 cases the colour index was found to be low in 17, high in 22 and normal in 36, and that as a rule the lower the red cell count the higher the colour index. A case recorded by Selling (1916) was an exception to this rule, having very profound anaemia (640,000 reds per c.mm.) with a low colour index (0·6).

The blood platelets

In nearly all cases where a platelet count has been made thrombopenia has been recorded, the platelets sometimes falling to levels less than $\frac{1}{60}$ of the normal, e.g., 4,000 per c.mm., in a case of Mitnik and Genkin (1931), 600 in one of Brocher (1929). These low values usually occur in cases with severe purpuric manifestations but not always. Hamilton (1931), for example, observed no haemorrhage in a case with marked loss of platelets, and Mitnik and Genkin reported haemorrhage with a normal platelet count. Nikulina and Titowa (1934) agree that reduction of the number of blood platelets does not always result in haemorrhagic symptoms (they record one case with a thrombocyte count of 18,790 per c.mm. with no signs of bleeding), but state that with a high degree of thrombopenia the tendency to haemorrhage increases, and that this tendency is dependent also upon the length of exposure, i.e., it is present chiefly in persons exposed to benzole for a short period in spite of comparatively high thrombocyte counts, while amongst those exposed for a long period, a tendency to haemorrhage

is only present with a high degree of thrombopenia. These workers found that when exposure to benzole is prolonged the thrombocyte count tends to increase, but they are unable to explain this finding.

They have also attempted to correlate the degree of thrombopenia with the leucopenia, anaemia, and relative lymphocytosis of typical chronic benzole poisoning, but have come to no more definite conclusions than that while no strict parallelism between these conditions can be postulated, thrombopenia is an earlier and more constant symptom than anaemia, that the number of thrombocytes tends to increase with a rising lymphocyte count, and that thrombopenia develops *pari passu* with leucopenia.

Blood Coagulation in Chronic Benzole Poisoning

According to Simonin (1934) the coagulation time may be normal or delayed. Hayhurst and Neiswander (1931) found that the coagulation time was 4 minutes in a case with bleeding from the skin and mucous membranes. Brindeau (1931) found it delayed in two cases with severe symptoms resembling pernicious anaemia and Rohner and co-workers (1926) estimated it at 9 minutes in a fatal case, but Dimmel (1933) observed no delay in a series of 66 cases of varying severity.

Coagulation itself, according to Simonin (1934), may be atypical, showing irretractability of the clot.

Bleeding time is also variable, but is apparently more often normal than prolonged. It was prolonged (25 minutes) in the case recorded by Hayhurst and Neiswander, and in those of Brindeau and of Rohner and co-workers. Dimmel states that with extreme thrombopenia it is prolonged, otherwise normal or doubtful.

Changes in the Bone-Marrow

The changes described in the bone-marrow in such cases as have come to autopsy are usually those of profound aplasia, affecting both the erythroblastic and the leucoblastic elements. In Selling's case injury to the latter was much greater than to the former, the marrow being practically depleted of leucocytes. In one of the cases recorded in the Home Office Report for 1918, the marrow was described as showing an aplastic anaemia, identical with that produced by trinitrotoluene poisoning, while in two other fatal cases the bone-marrow was converted into a "brownish, pasty mass" (1934) and "practically all replaced by yellow fat" (1931).

Evidence of regenerative processes, such as have been described in experimental animals, was not forthcoming in the case examined by Rohner, Baldridge, and Hausmann (1926), the bone-marrow containing few cells, but no megakaryocytes. "Marked haematopoietic insufficiency, as evidenced by leucopenia, low platelets and red blood cell counts was seen to be due to failure of the marrow cells to produce either granulocytes or megakaryocytes. The few bone-marrow cells present contained inclusions of pigment, some being obviously endothelial phagocytes and others resembling non-granular myelocytes."

Lesions of Internal Organs

In such lesions as have been observed in autopsies of fatal cases it is difficult, as pointed out by Litzner (1932), to decide whether they are due to direct injury by benzole or to secondary injury from severe blood changes.

Heart—myocardial infarcts (Lenoir and Claude, 1897) and fatty degeneration of the muscle (Selling, 1916) have been recorded, while in the two (1918) cases in the Home Office Reports haemorrhages were found under the endothelium of the heart.

Liver—fatty degeneration (Selling), areas of necrosis (Rohner and co-workers) and enlargement with excessive iron deposition (fatal case, Home Office Report, 1931).

Spleen.—The reports of post-mortem examinations of the spleen appear to show less change than in experimental animals. Landé and Kalinowsky (1928) found it small and anaemic, with no demonstrable histological lesions. In the 1931 Home Office fatal case the spleen showed excessive iron deposition. A spleen removed therapeutically by Hegler (1928) was very little enlarged; the sinuses were filled with erythrocytes and reticulo-endothelial cells.

Adrenals.—Petri (1926) states that the adrenals in benzole poisoning are deficient in fat and show areas of necrosis.

Gastro-intestinal tract.—In both the 1918 Home Office cases submucous haemorrhages were found throughout the intestinal tract, in the 1931 case melanosis and small ulcers of the large intestine, and in the 1934 case submucous haemorrhages of the stomach.

Differential Diagnosis of Benzole Poisoning

In differentiating benzole poisoning from the chief conditions in which leucopenia and anaemia are found together, it appears that the only indubitable distinguishing feature is a history of exposure to benzole. The criteria of the National Safety Council (1926) for benzole poisoning were as follows:—"A history of exposure to benzole and a white blood cell count below 5,600 is accepted as reasonable evidence of poisoning."

The three chief conditions from which benzole poisoning may have to be distinguished are: (1) Agranulocytosis; (2) Aplastic anaemia (idiopathic); (3) Thrombopenic purpura. Dimmel (1932) adds also septic aleukaemia, from which he states that benzole poisoning in its final stages, if accompanied by secondary infection, is practically indistinguishable.

In *agranulocytosis* according to Pulford (1931) the spongy oozing gums may ulcerate and become gangrenous and slough, which does not happen with benzole poisoning. Other differential diagnostic points are that in agranulocytosis fever is an early and persistent sign while in benzole poisoning it is usually terminal; the coagulation time, bleeding time, platelet count and retractility of clot are usually unaffected in agranulocytosis.

In *aplastic anaemia*, the symptoms and blood picture are very similar to those of benzole poisoning, but, according to Pulford, the duration of the disease is usually less.

In *thrombopenic purpura*, purpura is the more outstanding feature, while oozing is the more characteristic feature of benzole poisoning. In thrombopenic purpura also the spleen may be palpable and the white cell count is likely to be higher in the later stages than in those of benzole poisoning. These diagnostic features are also discussed by Sweeney (1928), Askey (1928), McCord (1929), Dameshek (1929) and Kracke (1932).

The following table showing the various diagnostic points has been drawn up by Pulford (1931).

	Benzole poisoning.	Agranulocytosis.	Thrombopenic purpura.	Aplastic anaemia.
R.B.C's reduced ..	+++	+	+	++
W.B.C's reduced ..	+++	++++	+	+++
Lymphocytes	+++	++++	.....	Normal
Platelet count reduced	++	----	+++++	+
Coagulation time increased.	----	-----	Normal	-----
Bleeding time increased	+	-----	+++	-----
Contractility of clot prolonged.	+	-----	+++	-----
Tourniquet test ..	++	-----	++++	-----
Spleen enlarged ..	-----	-----	++	-----
Reticulation of R.B.C's	+	-----	Normal	-----
Normoblasts	+	-----	-----	-----
Fragility of R.B.C's ..	-----		-----	-----

R.B.C. = Red blood corpuscles. W.B.C. = White blood corpuscles.

The following table shows the features of the blood picture found in the chief investigations published :—

Author.	W.B.C's, per c.mm.	Haemoglobin, per cent.	R.B.C's millions, per c.mm.	Thrombocytes, per c.mm.	Differential Count.	Other features.
Santesson (1897) ..	Leucopenia	80	3·7	—	—	—
		20	0·6			
Selling (1916) ..	480	8	0·64	Thrombopenia	—	—
McClure (1916) ..	1,100	25	1·46	Thrombopenia	—	—
Harrington (1917)..	500	60	2·8	—	—	—
Home Office Report (1918)	2,000	35	2·8	—	—	—
Newton (1920) ..	1,200	80	5·7	—	—	—
	1,250	—	3·6	—	—	—
	1,700	—	4·0	—	—	—
Pugliese (1922) ..	1,700	29	1·7	Thrombopenia	—	—
Hogan and Schrader (1923)	600	39	1·24	—	—	—
	104	12	0·9	—	56% lympho.	—
	950	16	0·88	—	52% lympho.	—
Hamilton (1931) ..	2,000	20	1·0	—	—	—
Brücken (1923) ..	2,460	32	1·51	24,240	42% lympho. 10% monocytes	—
	3,870	55	—	—	32% lympho.	(*Contd. on p.* 49.)

Author.	W.B.C's, per c.mm.	Haemoglobin, per cent.	R.B.C's millions, per c.mm.	Thrombocytes, per c.mm.	Differential Count.	Other features.
Teleky and Weiner (1924)	3,500	60	3·58	—	42% lympho.	—
Rohner *et al.* (1928)	1,400	20	0·85	70,000	48% lympho.	Aniso- and poikilocytosis.
Winslow (1927) ..	1,450–6,140	Under 30	0·8–5·4	—	Usually lymphocytosis	—
Ross Smith (1928)	Leucopenia	Reduced	Slightly reduced	—	Lymphocytosis myelocytes	—
Landé and Kalinowsky (1928)	2,000	35	1·0	34,000	76% lympho.	Anisocytosis.
	3,200	70	4·2	—	35% lympho.	Poikilocytosis, basophilia.
Laignel-Lavastine, *et al.* (1928)	600	20	1·24	42,000	51% monocytes	—
Brocher (1929) ..	2,000	11	0·63	6,000	39% lympho.	—
Schneider (1930) ..	4,640	47	2·2	114,000	44% lympho.	Nucleated r.b.c's.
	1,320	56	2·34	116,000	44% lympho.	Poikilocytosis, basophilia.
Sorrentini (1930) ..	3,000	80	2·6	—	—	—
Fischer (1932) ..	1,000	—	2·0	—	—	—
Adler-Herzmark (1930)	2,000–3,000	—	3·0	—	—	—
Hayhurst, *et al.* (1931)	850	10	0·9	100,000	—	Anisocytosis. Bleeding time 25 mins. Coagulation time 4 mins.
Brindeau (1931) ..	1,770	50	1·638	—	—	Monocytosis.
	1,300	22	0·9	—	—	Aniso- and poikilocytosis, nucleated R.B.C's.
Löwy (1926) ..	1,800	30	1·3	—	38% lympho.	—
	1,600	26	1·6	4,000	82% lympho.	Punctate basophilia.
Mitnik and Genkin (1931)	3,800	33	2·4	—	24% lympho.	—
	4,000	63	3·9	128,000	29% lympho.	Recticulocytes increased.
	4,300	69	4·1	—	29% lympho.	
	4,500	73	4·85	194,000	40% lympho.	
Espeut and Selinger (1930)	Slight leucopenia	Normal	Normal	—	32% and 50% lympho.	—
Kranenberg and Peters (1928)	More than 50% reduction	65	—	—	Over 39% lympho.	—
Nikulina and Titowa (1934)	4,737	70–79	3·5–4·0	19,283	Lymphocytosis	—
	6,300	70–79	3·5–4·0	25,497	Lymphocytosis	—
Meriden and Israel (1934)	2,700–8,600	60–85	2·5–4·5	3.800–230,000	20–55% lympho.	Monocytes, 3–22%. Myeloblasts, myelocytes.
Pulford (1931) ..	1,940	21	1·2	94,000	Lymphocytosis	Slight reticulocytosis.
Newton (1920) ..	1,200	80	4·7	—	—	Monocytes, 39%.
Dimmel (1932) ..	170–9,600	18–110	0·78–5·3	0–360,000	8–60% lymphocytosis	Monocytes up to 18%. Eosinophils up to 53%. Degenerated and young leucocytes; megalocytes.

Treatment of Chronic Benzole Poisoning

Therapeutic measures of various kinds have been tried, but apparently with little success if the poisoning has become severe. Dimmel (1932) states that it is not possible to save life by any means in cases of severe injury. The following measures have been tried :—

(1) *Blood transfusion* had no favourable effect in the hands of Dimmel, or of Nicolajew and Schparo (1929), especially with regard to the leucopenia. Dimmel observed many erythrophages in the blood of patients treated with transfusion, and considers that leucopoiesis is not likely to be stimulated in view of the blockading of these cells by such a process of phagocytosis.

(2) *Irradiation of the bone-marrow and spleen,* had no success in Dimmel's cases.

(3) *Splenectomy* was followed by recovery in a case reported by Hegler (1928).

(4) *Liver therapy, and a vitamin-rich diet* have been recommended in cases with a tendency to hyperchromic anaemia (Schneider, 1930; Dimmel, 1932, etc.)

(5) *Protein shock and adrenaline therapy*, with a view to stimulating the bone-marrow was also tried by Dimmel but with no definite results.

INVESTIGATIONS ON WORKERS EXPOSED TO BENZOLE WITHOUT DEFINITE SIGNS OF POISONING. (SEE TABLES I & II, pp. 53 & 54)

It might be expected that periodic observations of workers exposed to benzole vapour would show some indication, either by clinical symptoms or by abnormalities in the blood picture, of the early and insidious effects characteristic of true benzole poisoning. During recent years a number of such investigations have been carried out under the instructions of H.M. Chief Inspector of Factories, covering a wide range of industries in which benzole is used. Since a somewhat similar investigation has been conducted almost simultaneously in Germany by Meyer and Schneider (1933) it has been thought that a close comparison of the results might be of interest and value. The most striking point of difference is that the German workers appear to have suffered more severely and more frequently than the English. Whereas out of the 61 German workers investigated only 2 (i.e., 1·2 per cent.) showed no indication of injury to the haemopoietic system; out of 208 in which differential counts were made by the Home Office (between 1926 and 1935), 112 (i.e., 54 per cent.) showed no abnormality of the blood picture. The symptoms complained of, though slight, showed a correspondingly higher incidence in the German investigation.

The Industries Concerned

The German authors give no details of the industries in which their 61 workers were employed. The English workers in whom differential counts were made were employed as follows:—Cellulose spraying 53, powder mills 29, rubber manufacture 14, lens manufacture 18, motor upholstery 10, artificial silk 9, leather manufacture 8, colour printing 7, radio valve manufacture 7, Filling of cans 5, shoe manufacture 4, camera manufacture 2, aeroplane factory 41, filling tanks with benzole 1.

Symptoms

In the German investigations, slight symptoms, which included fatigue, stupor, headache, nausea, gastric disturbance, loss of appetite, intestinal disturbance and vomiting were complained of by all the workers examined. Loss of weight, to the extent of 4–13 pounds was observed in 7; nasal catarrh and slight nose bleeding in several, and eczema of the hands in 1. The majority looked pale and exhausted.

In the English investigation, 325 workers were questioned as to the occurrence of symptoms ; out of these, 197 (60·6) complained of no symptoms of any kind. Of the remaining 128 (39·4) the incidence of symptoms was as follows :—Fatigue in 18, gastric disturbances (including nausea) in 21, loss of appetite in 8, dizziness in 5, "light headedness" or "intoxication" in 6, headache or "heavy head" in 15, drowsiness in 12, slight nose bleeding in 8, slight gum bleeding in 5, haematuria in 1, haemoptysis in 1, amenorrhoea in 1, apparent anaemia in 13, pain in muscles in 7, dyspnoea in 2, conjunctivitis and sore throat in 5.

The Chief Differences in the Blood Picture

The chief differences in the results of the German and the English investigations in addition to the considerably higher incidence of abnormalities in the German workers were as follows :—

(1) Changes in the red cell count were more pronounced in the English investigation.

(2) Degenerative changes in the white cells were more pronounced in the German investigation.

(3) Leucocytosis occurred more frequently in the German investigation.

Relative lymphocytosis in association with a mild degree of leucopenia was a similar feature in both groups of workers.

The Total Red Cell Count, Haemoglobin Level and Condition of Red Cells

In the German workers, only slight changes in the red cell count were observed, the majority reaching a level of 4·2 to 4·8 millions per c.mm. The haemoglobin level in general followed the red cell count so that the colour index was less than 1, and the picture was that of a slight hypochromic anaemia, resembling chlorosis. Anisocytosis was seldom, and nucleated or polychromatophilic cells never, observed.

In the English investigation, anaemia was a more pronounced feature ; low red cell counts, from less than 3 millions to 4·8 millions per c.mm., occurring in 37 out of 82 cases in which total red cell counts were made (45 per cent.). In 2 cases counts higher than normal were found, in one case over 6 million. With regard to this case, Dr. Henry remarks that "we may be seeing here the early effect (increased number of red cells) of exposure to benzole fumes, since he has only been in the department nine months." Haemoglobin estimations were made in only 11 cases. In 2 of these the level was 50 and 60 per cent. respectively and in a third 45 per cent. Degenerative changes were more frequent than in the German investigations, anisocytosis and poikilocytosis occurring in 9 cases, and punctate basophilia in 13, while occasional normoblasts were observed in 5 cases.

The White Cells

Total count

In the German investigation leucopenia was not a striking feature, in fact in nearly half the cases (45 per cent.) there was a leucocytosis—

over 10,000 in 11 cases and between 8,000 and 1,000 in 16. When leucopenia occurred it was comparatively slight, being under, 5,000 in only two cases.

In the English cases also the incidence of leucopenia was low (in only 25 per cent. of the 87 cases in which a total white cell count was made), but the actual numbers of leucocytes in the cases affected reached a rather lower level, the majority being between 4,050 and 5,600. The lowest level reached was 2,750, in one case only. A leucocytosis occurred in 2 cases—11,900 and 14,650 respectively.

Differential count

In the German investigation the cases with leucopenia showed generally also a *relative lymphocytosis*, usually between 35 and 50 per cent., reaching 67·6 per cent. in one case only. *Monocytosis* was not a pronounced feature, the highest percentage reached (4·66 per cent.) being found only once. *Eosinophilia* was, however, a characteristic feature, being present in 36 per cent. of the cases, and reaching levels of 6, 8, and even 15 per cent. *Basophil leucocytes* were increased (more than 1 per cent., up to 4 per cent.) in 21 cases.

The English workers showed a similar correlation between slight leucopenia and relative lymphocytosis, but in some cases the latter occurred with no notable decrease in the total white cell count. The actual percentages of lymphocytes varied in most cases from 36 to 51 per cent., in one case only the percentage reached 68 per cent. *Monocytosis* occurred with some frequency, being over 3 per cent. in about 40 per cent. of the cases, and in a few cases up to 11 per cent. *Eosinophilia* was infrequent, being over 2 per cent. in only 2 cases. *Basophil leucocytes* were slightly increased (up to 2 per cent.) in 2 cases.

Changes in form of the white cells

The leucocytes.—In the German investigation degenerative changes in the leucocytes were not frequent. The neutrophils showed sometimes a displacement to the right (an indication of predominance of ageing cells) less often a displacement to the left. Non-segmented and immature forms were not observed. In the English investigation true degenerative changes were observed in only one case. In 4 cases in which " non-filament " forms of polynuclear leucocytes were examined (indicating immature cells), these were increased in 2 cases (17–19 per cent.—the normal is given as 12–16 per cent.).

The lymphocytes.—The German investigators lay emphasis on their observation of changes in the appearance of the lymphocytes, consisting of segmentation of the nuclei and vacuolation of the protoplasm, which they consider a sign of injury of the protoplasm. They also state that *plasma cells*, which do not occur in normal adult blood, were found in some cases. They regard these as indications of a specific irritation of the lymphocyte-forming tissues. In the English investigation the lymphocytes were described in 5 cases as " large cells of obviously immature appearance."

The Blood Platelets

In the German investigation the blood platelets were not examined, and in the English only in 3 cases. In 2 of these the blood platelets were " scanty ", in the third, a case showing leucocytosis, they were " excessive ".

Progress of Condition of Workers after Removal from Exposure

Examinations of workers after removal from exposure to benzole were few in both investigations. Among the German workers apparently only 2 were examined and with very different results. In one rapid recovery took place, in the other recovery was slow and far from complete. In the first, examination a fortnight after stoppage of work showed that the red cell count had risen from 4·8 millions to 5·38 millions per c.mm., the white cells from 6,800 to 7,800, while the lymphocytosis had decreased from 67 per cent. to 48 per cent. In the second, after two months, the red cell count had only risen from 4·18 to 4·2 millions, the white cells were still only 5,600 and the lymphocytosis was still 47·8 per cent.

Of the English workers 14 were re-examined after either improvement in conditions of ventilation (6 cases), substitution of xylole to some extent for the benzole used (7 cases) or removal from exposure (1 case). Of these only 3 showed an improvement in the leucopenia, but 12 in the differential count. The one worker who was entirely removed from exposure was also treated with iron and showed special improvement in the red cell count (from 3·09 to 5·4 millions per c.mm.) and in the haemoglobin level (from 45 per cent. to 94 per cent.).

TABLE I.—SHOWING INCIDENCE OF SYMPTOMS IN THE ENGLISH WORKERS

	Number of Workers.	Percentage.
No symptoms	197	60·7
Symptoms present	128	39·3
Gastric disturbance	21	16·3
Fatigue	18	14·1
Headache or " heavy head "	15	11·7
Apparent anaemia	13	10·2
Drowsiness	12	9·4
Loss of appetite	8	6·3
Slight nose bleeding	8	6·3
Pain in muscles	7	5·4
" Intoxication "	6	4·7
Slight gum bleeding	5	3·9
Dizziness	5	3·9
Conjunctivitis and sore throat ..	5	3·9
Dyspnoea	2	1·5
Haematuria	1	0·8
Haemoptysis	1	0·8
Amenorrhoea	1	0·8
Total number investigated ..	325	

TABLE II.—BLOOD FINDINGS IN THE ENGLISH WORKERS INVESTIGATED

Red Cells.						White Cells.					
Total Count (82 workers investigated).		Haemoglobin percentage (11 workers investigated).		Abnormal conditions (82 workers investigated).		Total Count (87 workers).		Differential Count (208 workers).		Special Features (208 workers).	
	%		%		%		%		%		
Normal	52·4	Normal	72·8	Normal ..	68·3	Normal ..	74·7	Normal ..	53·9	Monocytosis, 3–11 per cent.	39·9
3–4·8 millions ..	45·2	Below 65 per cent.	18·1	Aniso- and poikilocytosis ..	10·9	4,050–6,500 ..	24·2	Lymphocytosis, 31–51 per cent.	45·7	Eosinophilia, over 2 per cent.	0·9
Above 5 millions	2·4	Below 50 per cent.	9·1	Punctate basophilia ..	15·8	Below 3,500 ..	1·1	Lymphocytosis, 68 per cent. ..	0·4	Basophil cells increased ..	0·9
				Normoblasts ..	6·0					Toxic degenerative changes ..	0·4

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First to March 31st, 1920. 6*d*. (7*d*.); Second to September 30th, 1921 (with Analysis of Published Work). 1*s*. 6*d*. (1*s*. 8*d*.); Third to September 30th, 1922. 2*s*. (2*s*. 1½*d*.); Fourth to December 31st, 1923. 1*s*. 3*d*. (1*s*. 4*d*.); Seventh to December 31st, 1926. 9*d*. (10*d*.); Eighth to December 31st, 1927. 9*d*. (10*d*.); Ninth to December 31st, 1928. 9*d*. (10*d*.); Tenth to December 31st, 1929. 6*d*. (7*d*.); Eleventh to June 30th, 1931. 1*s*. 6*d*. (1*s*. 7½*d*.); Twelfth to June 30th, 1932. 1*s*. 0*d*. (1*s*. 1*d*.); Thirteenth to June 30th, 1933. 9*d*. (10*d*.); Fourteenth to June 30th, 1934. 9*d*. (10*d*.); Fifteenth to June 30th, 1935. 9*d*. (10*d*.); Sixteenth to June 30th, 1936. 9*d*. (10*d*.); Seventeenth to June 30th, 1937. 9*d*. (10*d*.)

The following reports are out of print and not included in the list, Nos. 25, 26, 28, 32, 34, 35, 36, 38, 42 and Annual Reports, Nos. 5 and 6.

REPORTS CLASSIFIED ACCORDING TO SUBJECT MATTER

(i). Hours of Work, Rest Pauses, etc.

No. 1.—The Influence of Hours of Work and of Ventilation on Output in Tinplate Manufacture, by H. M. Vernon. (1919.) 6*d*. (7*d*.)

No. 2.—The Output of Women Workers in relation to Hours of Work in Shell-making, by Ethel E. Osborne. (1919.) 6*d*. (7*d*.)

No. 5.—Fatigue and Efficiency in the Iron and Steel Industry, by H. M. Vernon. (1920.) 3*s*. (3*s*. 2*d*.)

No. 6.—The Speed of Adaptation of Output to altered Hours of Work, by H. M. Vernon. (1920.) 1*s*. (1*s*. 1*d*.)

No. 24.—A Comparison of different Shift Systems in the Glass Trade, by E. Farmer, R. C. Brooks and E. G. Chambers. (1923.) 1*s*. 6*d*. (1*s*. 7*d*.)

No. 41.—Rest Pauses in Heavy and Moderately Heavy Industrial Work, by H. M. Vernon and T. Bedford, assisted by C. G. Warner. (1927.) 9*d*. (10*d*.)

No. 47.—Two Studies on Hours of Work. I.—Five-Hour Spells for Women with reference to Rest Pauses, by H. M. Vernon and M. D. Vernon, assisted by I. Lorrain-Smith. II.—The Two-Shift System in certain Factories, by May Smith and M. D. Vernon. (1928.) 1*s*. 3*d*. (1*s*. 4*d*.)

References, hours of work and rest pauses also occur in Report No. 56.

(ii). Dexterity

No. 63.—Inspection Processes in Industry, by S. Wyatt and J. N. Langdon. (1932). 1*s*. (1*s*. 2*d*.)

No. 64.—A Classification of Vocational Tests of Dexterity, by A. E. Weiss Long and T. H. Pear. (1932.) 1*s*. 3*d*. (1*s*. 5*d*.)

No. 66.—An Experimental Study of Certain Forms of Manual Dexterity, by J. N. Langdon. (1932.) 1*s*. (1*s*. 2*d*.)

* For overseas agencies see last page.

No. 67.—Manual Dexterity: Effects of Training, by E. M. Henshaw, J. N. Langdon and P. Holman. (1933.) 1*s.* (1*s.* 2*d.*)

No. 73.—The Acquisition of Skill: Analysis of Learning Curves, by J. M. Blackburn. (1936.) 1*s.* 6*d.* (1*s.* 8*d.*)

(iii). Industrial Accidents

No. 4.—The Incidence of Industrial Accidents, with special reference to Multiple Accidents, by Major M. Greenwood and Hilda M. Woods. (1919.) 6*d.* (7*d.*)

No. 19.—Two Contributions to the Study of Accident Causation, by Ethel E. Osborne, H. M. Vernon and B. Muscio. (1922.) 1*s.* 6*d.* (1*s.* 7*d.*)

No. 55.—A Study of the Personal Qualities in Accident Proneness and Proficiency, by E. Farmer and E. G. Chambers. (1929.) 3*s.* (3*s.* 2*d.*)

No. 68.—Tests for Accident Proneness, by E. Farmer, E. G. Chambers and F. J. Kirk. (1933.) 9*d.* (10*d.*)

References to industrial accidents also occur in Reports Nos. 39 *and* 62.

(iv). Atmospheric Conditions

No. 11.—Preliminary Notes on Atmospheric Conditions in Boot and Shoe Factories, by W. D. Hambly and T. Bedford. (1921.) 3*s.* (3*s.* 2*d.*)

No. 18.—Two Investigations in Potters' Shops, by H. M. Vernon and T. Bedford. (1922.) 2*s.* 6*d.* (2*s.* 8*d.*)

No. 20.—A Study of Efficiency in Fine Linen Weaving, by H. C. Weston. (1922.) 1*s.* 6*d.* (1*s.* 7*d.*)

No. 21.—Atmospheric Conditions in Cotton Weaving, by S. Wyatt. (1923.) 2*s.* (2*s.* 1*d.*)

No. 37.—Fan Ventilation in a Humid Weaving Shed. An Experiment carried out for the Departmental Committee on Humidity in Cotton Weaving, by S. Wyatt, assisted by J. A. Fraser and F. G. L. Stock. (1926.) 1*s.* 9*d.* (1*s.* 10*d.*)

No. 39.—The Relation of Atmospheric Conditions to the Working Capacity and the Accident Rate of Miners, by H. M. Vernon and T. Bedford, assisted by C. G. Warner. (1927.) 1*s.* 3*d.* (1*s.* 4*d.*)

No. 46.—A Physiological Investigation of the Radiant Heating in Various Buildings, by H. M. Vernon and M. D. Vernon, assisted by I. Lorrain-Smith. (1928.) 2*s.* (2*s.* 2*d.*)

No. 48.—Artificial Humidification in the Cotton Weaving Industry. Its Effect upon the Sickness Rates of Weaving Operatives, by A. Bradford Hill. (1927.) 2*s.* 6*d.* (2*s.* 8*d.*)

No. 58.—A Study of Heating and Ventilation in Schools, by H. M. Vernon and T. Bedford, assisted by C. G. Warner. (1930.) 2*s.* 6*d.* (2*s.* 8*d.*)

No. 59.—Sickness amongst Operatives in Lancashire Cotton Spinning Mills, by A. Bradford Hill. (1930.) 1*s.* 6*d.* (1*s.* 8*d.*)

No. 60.—The Atmospheric Conditions in Pithead Baths, by H. M. Vernon and T. Bedford (assisted by C. G. Warner). (1930.) 9*d.* (10*d.*)

No. 76.—The Warmth Factor in Comfort at Work, by T. Bedford. (1936.) 2*s.* (2*s.* 2*d.*)

References to atmospheric conditions also occur in Reports Nos. 1, 5, 22, 24, 51.

(v). Vision and Lighting

The Relation between Illumination and Efficiency in Fine Work (Typesetting by Hand), by H. C. Weston and A. K. Taylor. Joint Report of the Industrial Fatigue Research Board and the Illumination Research Committee. (1926.) 6*d.* (7*d.*)

The Effect of Different Systems of Lighting on Output and Accuracy in Fine Work (Typesetting by Hand), by H. C. Weston and A. K. Taylor, Joint Report of the Industrial Fatigue Research Board and the Illumination Research Committee. (1928.) 4*d.* (5*d.*)

The Relation between Illumination and Industrial Efficiency—The Effect of Size of Work. Joint Report of the Industrial Health Research Board and the Illumination Research Committee. (1935.) 4*d.* (5*d.*)

The Effect of Lighting on Efficiency in Rough Work, by S. Adams. Joint Report of the Industrial Health Research Board and the Illumination Research Committee. (1935.) 4*d.* (5*d.*)

No. 40.—The Effect of Eyestrain on the Output of Linkers in the Hosiery Industry, by H. C. Weston and S. Adams. (1927.) 1*s.* (1*s.* 1*d.*)

No. 49.—On the Relief of Eyestrain amongst Persons performing very fine Work, by H. C. Weston and S. Adams. (1928.) 1*s.* 3*d.* (1*s.* 4*d.*)

No. 57.—Further Experiments on the Use of Special Spectacles in very fine Processes. 1*s.* 3*d.* (1*s.* 4*d.*)

References to vision or lighting also occur in Reports Nos. 9, 20, 23.

(vi). Vocational Guidance and Selection

No. 12.—Vocational Guidance (a Review of the Literature), by B. Muscio (1921.) 1*s.* (1*s.* 1*d.*)

No. 16.—Three Studies in Vocational Selection, by B. Muscio and E. Farmer. (1922.) 1*s.* 6*d.* (1*s.* 8*d.*)

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No. 74.—The Prognostic Value of Some Psychological Tests, by E. Farmer and E. G. Chambers. 9*d.* (10*d.*)

No. 78.—A Borstal Experiment in Vocational Guidance, by Alec Rodger. (1937.) 9*d.* (11*d.*)

References to vocational selection also occur in Report No. 64.

(vii). Time and Movement Study, Methods of Work

No. 3.—A Study of Improved Methods in an Iron Foundry, by C. S. Myers. (1919.) 2*d.* (3*d.*)

No. 7.—Individual Differences in Output in the Cotton Industry, by S. Wyatt. (1920.) 6*d.* (7*d.*)

No. 8.—Some Observations on Bobbin Winding, by S. Wyatt and H. C. Weston. (1920.) 1*s.* 6*d.* (1*s.* 7*d.*)

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No. 56.—The Effects of Monotony in Work, by S. Wyatt and J. A. Fraser (assisted by F. G. L. Stock). (1929.) 2*s.* (2*s.* 1*d.*)

No. 72.—Incentives: Some Experimental Studies, by C. A. Mace. (1935.) 1*s.* (1*s.* 2*d.*)

No. 77.—Fatigue and Boredom in Repetitive Work by S. Wyatt and J. N. Langdon (assisted by F. G. L. Stock). (1937.) 1*s.* 3*d.* (1*s.* 5*d.*)

(viii). Posture and Physique

No. 29.—The Effects of Posture and Rest in Muscular Work, by E. M. Bedale and H. M. Vernon. (1924.) 2*s.* 6*d.* (2*s.* 8*d.*)

No. 36.—On the Design of Machinery in relation to the Operator, by L. A. Legros and H. C. Weston. (1926.) 2*s.* 6*d.* (2*s.* 7*d.*)

No. 44.—The Physique of Women in Industry (A Contribution towards the Determination of the Optimum Load), by E. P. Cathcart, E. M. Bedale, C. Blair, K. Macleod and E. Weatherhead, with a special section by S. G. Overton. (1927.) 5*s.* (5*s.* 2*d.*)

No. 50.—The Physiological Cost of the Muscular Movements involved in Barrow Work, by G. P. Crowden. (1928.) 1*s.* (1*s.* 1*d.*)

No. 71.—The Physique of Man in Industry, by E. P. Cathcart, D. E. R. Hughes, and J. G. Chalmers. (1935.) 1*s.* 3*d.* (1*s.* 5*d.*)

References to posture, etc., occur also in Reports Nos. 15 *and* 16.

(ix). Sickness and Absenteeism

No. 51.—A Study of Absenteeism in a Group of Ten Collieries, by H. M. Vernon and T. Bedford (assisted by C. G. Warner). (1928.) 2*s.* 6*d.* (2*s.* 8*d.*)

No. 54.—An Investigation into the Sickness Experience of Printers (with special reference to the Incidence of Tuberculosis), by A. Bradford Hill. (1929.) 4*s.* 6*d.* (4*s.* 8*d.*)

No. 62.—Two Studies of Absenteeism in Coal Mines, by H. M. Vernon and T. Bedford. 1*s.* (1*s.* 1*d.*)

No. 75.—Sickness Absence and Labour Wastage. Part I, by May Smith and M. A. Leiper. Part II, by Major Greenwood and May Smith. 1*s.* 3*d.* (1*s.* 5*d.*)

No. 79.—An Investigation into the Sickness Experience of London Transport Workers, with special reference to Digestive Disturbances, by A. Bradford Hill. (1937.) 6*d.* (7*d.*)

(x). Miscellaneous

No. 10.—Preliminary Notes on the Boot and Shoe Industry, by J. Loveday and S. H. Munro. (1920.) 1*s.* 6*d.* (1*s.* 7*d.*)

No. 13.—A Statistical Study of Labour Turnover in Munition and other Factories, by G. M. Broughton, E. H. Newbold, and E. C. Allen. (1921.) 3*s.* (3*s.* 2*d.*)

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No. 45.—Two Contributions to the Experimental Study of the Menstrual Cycle. I.—Its Influence on Mental and Muscular Efficiency, by S. C. M. Sowton and C. S. Myers. II.—Its Relation to General Functional Activity, by E. M. Bedale. (1928.) 2*s.* 6*d.* (2*s.* 8*d.*)

No. 65.—Two Studies in the Psychological Effects of Noise. I.—Psychological Experiments on the Effects of Noise, by K. G. Pollock and F. C. Bartlett. II.—The Effect of Noise on the Performance of Weavers, by H. C. Weston and S. Adams. (1932.) 1*s.* 3*d.* (1*s.* 5*d.*)

No. 70.—The Performance of Weavers under Varying Conditions of Noise, by H. C. Weston and S. Adams. (1935.) 6*d.* (7*d.*)

No. 80.—Toxicity of Industrial Organic Solvents. Summaries of published work compiled by Ethel Browning. (1937.)

REPORTS CLASSIFIED ACCORDING TO INDUSTRY

NOTE.—Most of the reports in the following list deal exclusively with the industries under which they are placed. In certain instances, however, reports have been prepared on some general subject, but yet make sufficient reference to a particular industry to justify inclusion under the appropriate heading. These reports are distinguished by an *. Reports which have no application to particular industries are not included in this section.

A.—MINING INDUSTRY

No. 39.—The Relation of Atmospheric Conditions to the Working Capacity and Accident Rates of Miners. 1*s.* 3*d.* (1*s.* 4*d.*)

No. 51.—A Study of Absenteeism in a Group of Ten Collieries. 2*s.* 6*d.* (2*s.* 8*d.*)

No. 60.—The Atmospheric Conditions in Pithead Baths. 9*d.* (10*d.*)

No. 62.—Two Studies of Absenteeism in Coal Mines. 1*s.* (1*s.* 1*d.*)

B.—METAL AND ENGINEERING INDUSTRIES

No. 1.—The Influence of Hours of Work and of Ventilation on Output in Tinplate Manufacture. 6*d.* (7*d.*)

No. 2.—The Output of Women Workers in Relation to Hours of Work in Shell-making. 6*d.* (7*d.*)

No. 3.—A Study of Improved Methods in an Iron Foundry. 2*d.* (3*d.*)

No. 5.—Fatigue and Efficiency in the Iron and Steel Industry. 3*s.* (3*s.* 2*d.*)

*No. 6.—The Speed of Adaptation to Altered Hours of Work. 1*s.* (1*s.* 1*d.*)

No. 15.—Motion Study in Metal Polishing. 2*s.* (2*s.* 1*d.*)

C.—TEXTILE INDUSTRIES

No. 7.—Individual Differences in Output in the Cotton Industry. 6*d.* (7*d.*)

No. 8.—Some Observations on Bobbin Winding. 1*s.* 6*d.* (1*s.* 7*d.*)

No. 9.—A Study of Output in Silk Weaving during the Winter Months. 2*s.* 6*d.* (2*s.* 8*d.*)

No. 17.—An Analysis of the Individual Differences in the Output of Silk-Weavers. 1*s.* 6*d.* (1*s.* 7*d.*)

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No. 21.—Atmospheric Conditions in Cotton Weaving. 2*s.* (2*s.* 1*d.*)

No. 23.—Variations in Efficiency in Cotton Weaving. 3*s.* (3*s.* 2*d.*)

No. 37.—Fan Ventilation in a Weaving Shed. 1*s.* 9*d.* (1*s.* 10*d.*)

No. 40.—The Effect of Eyestrain on the Output of Linkers in the Hosiery Industry. 1*s.* (1*s.* 1*d.*)

No. 48.—Artificial Humidification in the Cotton Weaving Industry. Its Effect upon the Sickness Rates of Weaving Operatives. 2*s.* 6*d.* (2*s.* 8*d.*)

*No. 49.—On the Relief of Eyestrain amongst Persons Performing very Fine Work. 1*s.* 3*d.* (1*s.* 4*d.*)

No. 59.—Sickness amongst Operatives in Lancashire Cotton Spinning Mills. 1*s.* 6*d.* (1*s.* 8*d.*)

No. 70.—The Performance of Weavers under Varying Conditions of Noise. 6*d.* (7*d.*)

D.—Boot and Shoe Industry

No. 10.—Preliminary Notes on the Boot and Shoe Industry. 1*s.* 6*d.* (1*s.* 7*d.*)

No. 11.—Preliminary Notes on Atmospheric Conditions in Boot and Shoe Factories. 3*s.* (3*s.* 8*d.*)

E.—Pottery Industry

No. 18.—Two Investigations in Potters' Shops. 2*s.* 6*d.* (2*s.* 8*d.*)

F.—Laundry Industry

No. 22.—Some Studies in the Laundry Trade. 2*s.* 6*d.* (2*s.* 8*d.*)

G.—Glass Industry

No. 24.—A Comparison of Different Shift Systems in the Glass Trade. 1*s.* 6*d.* (1*s.* 7*d.*)

H.—Letterpress Printing Industry

*No. 16.—Three Studies in Vocational Selection. 1*s.* 6*d.* (1*s.* 7*d.*)

*No. 26.—On the Extent and Effects of Variety in Repetitive Work.
The Relation between Illumination and Efficiency in Fine Work (Typesetting by Hand).
The Effects of Different Systems of Lighting on Output and Accuracy in Fine Work (Typesetting by Hand). 1*s.* 6*d.* (1*s.* 7*d.*)

No. 54.—An Investigation into the Sickness Experience of Printers (with special reference to the Incidence of Tuberculosis). 4*s.* 6*d.* (4*s.* 8*d.*)

I.—Transport Workers

No. 79.—An investigation into the Sickness Experience of London Transport Workers, with special reference to Digestive Disturbances. 6*d.* (7*d.*)

J.—Light Repetition Work

No. 14.—Time and Motion Study. 2*s.* (2*s.* 2*d.*)

No. 25.—Two Contributions to the Study of Rest Pauses in Industry. 1*s.* 6*d.* (1*s.* 7*d.*)

No. 26.—On the Extent and Effects of Variety in Repetitive Work. 1*s.* 6*d.* (1*s.* 7*d.*)

No. 30.—An Experimental Investigation into Repetitive Work. 2*s.* 6*d.* (2*s.* 7*d.*)

No. 32.—Studies in Repetitive Work with special reference to Rest Pauses. 2*s.* 6*d.* (2*s.* 7*d.*)

No. 52.—The Comparative Effects of Variety and Uniformity in Work. 1*s.* 3*d.* (1*s.* 4*d.*)

K.—Muscular Work

No. 29.—The Effects of Posture and Rest in Muscular Work. 2*s.* 6*d.* (2*s.* 7*d.*)

No. 41.—Rest Pauses in Heavy and Moderately Heavy Industrial Work. 9*d.* (10*d.*)

No. 44.—The Physique of Women in Industry. (A Contribution towards the Determination of the Optimum Load.) 5*s.* (5*s.* 2*d.*)

No. 50.—The Physiological Cost of the Muscular Movements involved in Barrow Work. 1*s.* (1*s.* 1*d.*)

No. 71.—The Physique of Man in Industry. 1*s.* 3*d.* (1*s.* 5*d.*)

SPECIAL REPORTS OF THE MEDICAL RESEARCH COUNCIL ON SUBJECTS RELATED TO THE BOARD'S WORK

Alcohol

No. 56.—The Effects of Alcohol and some other Drugs during Normal and Fatigued Conditions. By W. McDougall and May Smith. (1920.) 1*s.* (1*s.* 1*d.*)

Miners' Diseases, etc.

No. 89.—Report on Miners' "Beat Knee," "Beat Hand," and "Beat Elbow." By E. L. Collis and T. L. Llewellyn. (1924.) 1*s.*6*d.* (1*s.*7*d.*)

No. 80.—Second Report of the Miners' Nystagmus Committee. (1923.) 9*d.* (10*d.*)

No. 176.—Third Report of the Miners' Nystagmus Committee. (1932.) 9*d.* (10*d.*)

Nutrition

No. 87.—Report on the Nutrition of Miners and their Families. By the Committee upon Quantitative Problems in Human Nutrition. (1924.) 1*s.* 3*d.* (1*s.* 4*d.*)

No. 151.—A Study in Nutrition. An Inquiry into the Diet of 154 Families of St. Andrews. By E. P. Cathcart and A. M. T. Murray, assisted by M. Shanks. (1931.) 1*s.* (1*s.* 2*d.*)

No. 165.—Studies in Nutrition. An Inquiry into the Diet of Families in Cardiff and Reading. By E. P. Cathcart and A. M. T. Murray, assisted by M. Shanks. (1932.) 6*d.* (7*d.*)

Dust

No. 199.—Physical Methods for the Estimation of the Dust Hazards in Industry. By H. L. Green and H. H. Watson. (1935.) 1*s.* (1*s.* 2*d.*)

OTHER PUBLICATIONS IN 1936–37

BEDFORD, T.: "Requirements for satisfactory Ventilation and Heating". *Hum. Factor, Lond.*, 1936, **10**, 245.

"Warmth and Comfort." *J. Instn. Heat. and Vent. Engrs.*, 1936, **4**, 383.

"Ventilation and heating in Relation to Comfort." *Industr. Welf.*, 1937, **19**, 218, 13.

"Modern Principles of Ventilation and Heating." *H. K. Lewis & Co., Ltd., London*, 1937.

CULPIN, MILLAIS: "Psychological Disorders in Industry." *Practitioner*, 1936, **137**, 324.

"The Application of Medical Psychology in Industry." *Med. Off.*, March, 1937.

FARMER, E.: "The Human Factor in Accident Causation." *J. Insur. Inst. Lond.*, 1937, **29**, 1.

LANGDON, J. N.: "A Two-factor Study of Simple Motor Tests with Particular Reference to Practice and Prognosis." *Brit. J. Psychol.*, 1937, **27**, 4.

SMITH, MAY: "Nerves as a Handicap to Efficiency." *Ment. Welf.*, **17**, 65.

"The Temperamental Factor in Industry." *Engineering*, 1936, **129**, 3622.

"The Temperamental Factor in Industry." *Hum. Factor, Lond.*, September, 1936.

"Psychology in Industry." *Brit. Med. J.*, 1937, i., 503.

WESTON, H. C.: "Machine Design and the Welfare of the Operator." *Industr. Welf.*, 1937, **19**, 217.

"Industrial Lighting." *J. Inst. Production Engrs.*, 1937, **16**, 4.

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