419. Davies, T.A.L. (Dept. Employment and Productivity, London, England): Hunter, C.G. (Tunstall Lab., Sittingbourne, Kent, England): Williams, M.K. (London School Hyg. and Trop. Med., England): THE EARLY DETECTION OF ABSORPTION OF TOXIC MATERIALS. Proceedings of the Royal Society of Medicine 61:911-2; 913-5; 915-6(Sept.), 1968.

Section of Occupational Medicine

President W Melville Arnott TD FRCP

Meeting February 8 1968

The Early Detection of Absorption of Toxic Materials [*Abridged*]

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Control of Toxic Hazards

The anecdotal collection of cases of poisoning is no longer a sufficient index of industrial environment. Because of the lack of screening tests, we may be compelled (for diseases such as anthrax or occupational cancer) to rely on the diagnosis of overt disease. So far as cancer is concerned, the safety of environment can only be determined by lifetime studies of 'at risk' populations. An example of a lifetime study is the register of 42,105 men (after excluding those born outside UK) who were aged 35 years and had been employed for one year or more in 380 rubber and cable factories (of which 128 had used renal tract carcinogens), which was established by a census on February 1, 1967. The experience of these men will be followed by watching removals from the NHS register (to determine the cause of death) and registrations with cancer bureaux for defined cancers (ICD (Eighth Revision) 150, 155, 188, 189, 191, 192, 204–7). Other registers established by the Medical Branch of HM Factory Inspectorate concern workers exposed to benzene (though it is recognized that the past widespread use of benzene renders the completeness of this register questionable), blowroom and card-room operatives in coarse cotton mills in Lancashire, persons reported as suffering from or dying of mesothelioma, and chrome platers in selected areas.

The traditional example of success in reducing poisoning is the reduction from 1,058 notified cases of lead poisoning in 1900 to a current yearly total of 80–100 notified cases. Quite apart from considerable under-notification, it will be shown that the more refined screening tests are used, the greater is the iceberg below the surface.

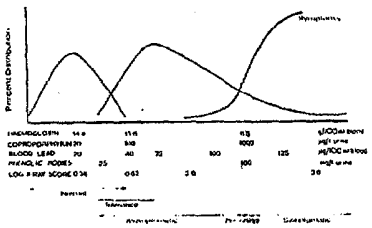

Fig 1 *Distribution of normal and abnormal vital observation in relation to symptoms of haemoglobin, urinary coproporphyrin and blood lead in lead workers, phenolic bodies in urine of workers absorbing benzene and X-ray score in foundry workers*

Fig 1 shows the distribution of vital observations in persons not exposed and occupationally exposed to various toxic agents. Any person having relevant vital observations outside the normal range must be regarded as showing a metabolic response to environment. This is clearly demonstrated by the distribution of hæmoglobin in asymptomatic lead workers (Fig 3). Clearly, when overt symptoms and signs develop – which may be predicted if individual and group observations exceed defined levels – poisoning occurs. Between symptomatic poisoning and the accepted higher limit of normality there is an area of abnormality which, if not justifying the term symptomatic poisoning, represents a departure from normal, often a potentially hazardous departure, for which the term asymptomatic poisoning is suitable. The difficulty is to judge what is significant; it may be argued that blood lead up to 80 µg/100 ml, or an X-ray score[1] in foundrymen from 0·63 to 1·0, represents no more than retention. Further, retention above these levels may not cause immediate harm, but no one

[1]A score based on readings by three observers, using inter-observer differences

can say when symptomatic anaemia due to lead, or progressive pneumoconiosis in a foundry worker, or blood dyscrasia in a worker excreting more than 100 mg/l of phenolic bodies in the urine, may ensue. My basic contention is that persons in this area must be regarded as at risk, until over a lifetime we have shown that neither efficiency, morbidity nor mortality are affected. Ultimately, these questions can only be solved by establishing 'at risk' registers, and observing persons on the registers until death. It must be remembered that the objective is an environment judged safe by the most sophisticated methods; to this end, serial vital observations of the most sophisticated kind should, whilst the lifetime study is being undertaken, be compared with relevant and biologically significant environmental observations.

The question arises what part, if any, routine medical examinations have to play in contributing to the early diagnosis of occupational ill health, and if they have a part, what standards should be adopted? If the diagnosis of lead poisoning is to be maintained at the symptomatic level – and this has been shown above to be a wholly unacceptable level – hæmoglobin gives a much better 'cut off' in relation to blood lead than urinary coproporphyrin (Figs 2 & 3). The idea of poisoning requiring symptoms or signs for its diagnosis is one that we must get rid of. What we have to

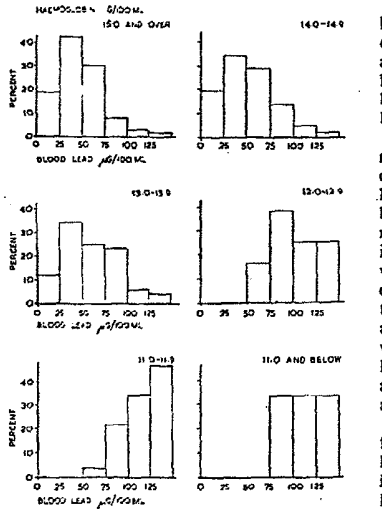

Fig 2 *Relationship between blood lead and hæmoglobin in 600 lead workers (Lloyd Davies 1966)*

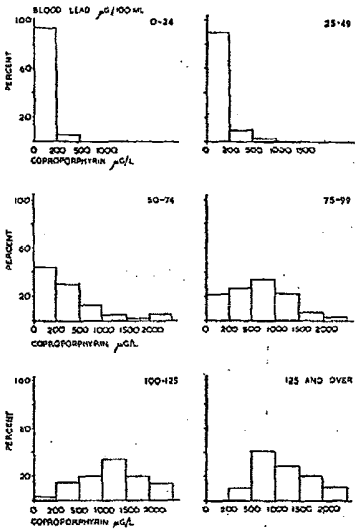

Fig 3 *Relationship between blood lead and urinary coproporphyrin excretion in 600 lead workers (Lloyd Davies 1966)*

look at is the distribution of relevant vital observations. Might not adequate – and the word adequate is emphasized – relevant and biologically significant environmental sampling combined with selective medical examination be better?

Medical supervision without the rigid enforcement of standards may, if we are not careful, become a hindrance to industrial health. To take lead as an example, a workman who has a blood lead of 80 µg/100 ml whole blood or higher is at risk. Further, the environment in which he works is unsafe – and no amount of argument as to whether he is suffering from poisoning or not will effect an improvement in environment. If I say that he is suffering, to say the least, from an unacceptable level of lead retention, I would not wish to be interpreted as regarding levels of blood lead of less than 80 µg/100 ml as always acceptable. Such cases should be notified as being asymptomatically poisoned.

In my view, there are two long overdue needs, first to develop screening tests based on improved knowledge of the detoxication and metabolism of industrial poisons, and secondly to provide for lifetime studies.

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Dr C G Hunter
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Solvents with Reference to Studies on the Pharmacodynamics of Benzene

High-risk workpeople are those who are hyperexposed and those who are hypersusceptible. It is important to detect the highly exposed workers during contact with the liquid and vapour forms of solvents such as ketones, aromatics and the chlorinated hydrocarbons. During post-exposure situations, the value of analyses of expired air for the presence and concentrations of some of these materials in industrial and hospital practice has been reported (Stewart *et al.* 1963, Stewart & Boettner 1964). The methodology of detection and the estimates of intensities of the exposures are based on studies of the pharmacodynamics of the solvents in man as determined in volunteer subjects. Such information is not available for industrial exposures to benzene and this contribution considers the early detection of absorption of the vapour of benzene by newer methods.

The absorption of any material by man is recognized by finding the material or its metabolites in the tissues and excretions of the body. In the case of the solvent benzene there are no endogenous sources, and the detection of benzene in tissues and excretions is positive evidence of exposure. However, exogenous and endogenous sources of its metabolites exist which need evaluation when exposure to benzene is assessed on the excretion of the metabolite phenol. Studies are being made of defined exposures in man to relate the results of analyses of expired air and urine for benzene and its metabolites with the intensities of the exposures. In these, adult male subjects have been exposed to concentrations of the vapour of benzene ranging from 90·0 to 2,250 mg/m³ for periods of 1–4 hours at energy expenditures of 0·17–0·69 kcal/kg/10 min, and the absorption and elimination of benzene and urinary phenol measured.

Elimination of Benzene Vapour in Expired Air

A steady rate of absorption of benzene occurs quickly after the start of an exposure, the time to attain this state and the proportion of the exposure dose absorbed being a reflection of the individual and the energy expenditure (to be reported). At the end of several exposures to concentrations of benzene vapour of the order of 300 mg/m³ (100 ppm), four times the threshold limit value, the expired air contained concentrations of 180–220 mg/m³. When exposure ceased, there was a rapid fall in the concentrations of benzene, but benzene could be detected in exhalations up to twenty-four hours after exposure with an instrument sensitive to 0·02 mg/m³ (Fig 1). Thus, the detection of benzene in expired air after

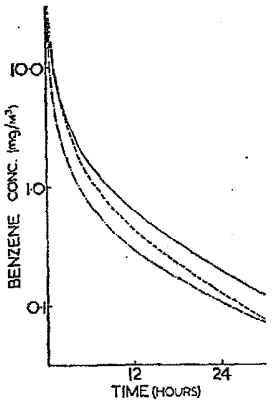

Fig 1 *Concentrations of benzene vapour in expired air after defined exposure to the vapour at a concentration of approximately 300 mg/m³*

industrial exposures is possible and an indication of the intensity of the industrial exposure may be obtained from the concentrations found at known times after work. Currently, defined exposures are being made to lower concentrations of the vapour of benzene to plot concentration/time values for benzene in post-exposure exhalations. Further, the concentrations of benzene vapour in end-tidal air will indicate the tensions of benzene in blood and give a measure of the body burden of benzene. This body burden may become the important parameter in the assessment of allowed burdens of toxicants, in this case, arising from industrial exposures.

Excretion of the Metabolite Phenol in the Urine

For several years exposures to benzene have been detected and their intensities estimated by analyses of the urine for the main urinary metabolite, phenol (Docter & Zielhuis 1967). However, the older methods of detecting urinary phenol are not specific and phenol is a constituent of normal urine. Thus, many of the findings of earlier work remain questionable. To assess more accurately the normal urinary excretion of phenol and to relate the excess excretion to defined exposures, specific methods of analysis have been used (Van Haaften & Sie 1965). The excretion of phenol in 100 samples of urine, grab or consecutive, obtained over periods of 0·5–48·0 hours in 12 men without exposure (as far as is known) to benzene or chemicals likely to be metabolized to phenol, was measured. A mean concentration of 8·0 mg/l and a range of concentrations from <1·3 to 41·7 mg/l, uncorrected for specific gravity or osmolality, were found. To overcome the difficulty of

correcting for urine volume, the hourly rate of phenol excretion was determined in the same samples giving a mean value of 0·41 mg phenol/hour, about 9·5 mg phenol/man/day, with a range of <0·03–2·27 mg/hour.

Since grab samples of urine are tested for phenol in the detection of exposures to benzene and in the estimations of their intensities, a knowledge of the basal excretion of urinary phenol is needed for each workperson. The rates of basal excretion of urinary phenol have been measured in several unexposed subjects over forty-eight hours, the samples of urine being apportioned into collections for three periods of the day, morning, afternoon/evening and overnight. The values ascertained in some were compared with the rates of excretion of creatinine over the same periods (Fig 2). It is apparent that the rate of excretion of phenol in the urine is very variable and not as constant a physiological process as that of the excretion of creatinine in the urine. Thus, for the individual worker, not only volumes of urine but also basal ranges of diurnal rates of excretion should be known when measuring urinary phenol excretion in respect to exposure to benzene.

In some of the defined exposures mentioned above, measurements have been made of the urinary excretion of phenol in respect to the intensities of the exposures (Table I). The rates of excretion of phenol measured during the exposures increased by factors varying from 4 to 20 and some became higher during the first four hours after exposure ceased. The concentrations, uncorrected for volumes of urine, likewise increased, the highest value for each subject ranging from 42·0 to 223·0 mg/l.

In occupational medical practice, estimates are made of the intensities of exposures to benzene during work by analysing grab samples of urine at the end of work shifts which may last eight hours. The values of the rates of excretion of urinary phenol at the end of the short defined exposures of these studies are not applicable to the situations in industry with longer exposures. Furthermore, the higher rates of excretion found some hours after exposure suggested that a steady state of metabolism had not been reached in defined exposures lasting up to two hours, even

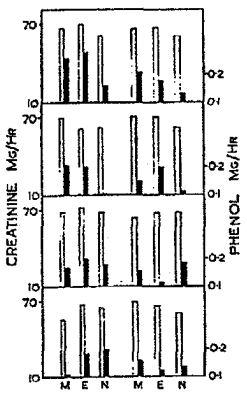

Fig 2 *Diurnal rates of urinary excretion of creatinine (open columns) and phenol (blocked columns) morning (M), afternoon/evening (E) and overnight (N)*

though a steady state of absorption occurs very quickly. To ascertain the length of exposure required to reach a steady state of metabolism of benzene to phenol, exposures of two to four hours have been made in one subject to concentrations of benzene nearer the threshold limit value. Over this time a steady state in respect to absorption is witnessed by the relationships between the con-

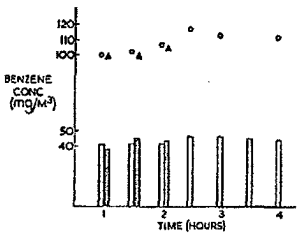

Fig 3 *The concentrations of benzene vapour in inhaled air (symbols) and exhaled air (columns) during 2-hour (hatched symbols and columns) and 4 hour (open symbols and columns) exposures of a standing subject*

Table I

The exposure, urinary excretion of phenol, maximum normal value, during and after exposure of 4 adult males

	Exposure		*Urinary excretion of phenol (mg/hour)*					
Subject No.	*Conc. (mg/m³)*	*Time (hours)*	*Maximum normal value*	*Exposure*	*Time post-exposure (hours)* 0–4	4–8	8–20	20–24
1	308·0	1·0	0·87	1·15	5·98	2·26–3·72	0·65	1·15
2	327·0	1·0	0·26	2·25	1·251	1·86	1·03	0·75
3	347·0	1·0	0·16	3·04	4·84	2·25–3·13	0·64	0·67
4	306·0	1·0	2·27	4·13	2·33	3·82	2·34	2·92
	295·0	2·0	2·27	3·43	6·37	3·29	2·11	1·81
					8·23			

centrations of benzene in the inhalations and exhalations (Fig 3), some 55–60% of the inhaled benzene being absorbed. A steady state of metabolism to phenol did not occur in two hours, and required in this subject 2½–3 hours (Figs 4, 5). The rates of excretion of urinary phenol expressed as mg/man/day for a continuing exposure to benzene vapour at a concentration of 100 mg/m³ approximate to 100 mg/man/day, a value of the order of that calculated for industrial exposures of this intensity (Docter & Zielhuis 1967).

In detecting exposures to the solvent benzene and estimating their intensity, the necessity for determinations made on man is obvious. The presence of benzene in expired air after exposure has ceased is definite evidence of exposure, but as yet the present studies are not able to relate the results of post-exposure analyses of expired air at known times after work with the concentrations of benzene respired at the workplace. More deliberate exposures to defined concentrations are needed. However, in determining the rates of excretion of urinary phenol for defined exposures to benzene vapour, exposures of four hours or more are essential, owing to the time required to reach a steady state of metabolism.

The early detection of absorption of toxic materials like solvents can be made by the analyses of tissues and body fluids for the presence of the materials or their metabolites. Where the toxic materials are absorbed in vapour form and excreted in vapour form, the analyses of post-exposure samples of expired air involve no difficult procedures for the workmen to undergo, give proof of exposures and may help in defining

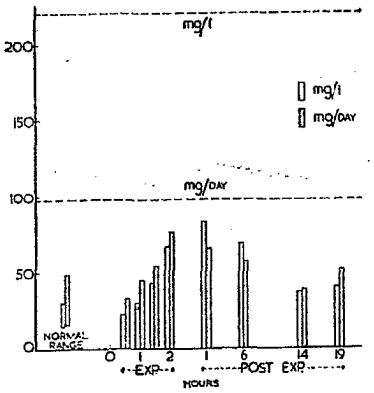

Fig 4 *Half-hourly urinary excretion of phenol during and after defined exposure to benzene vapour at a concentration of approximately 100 mg/m³ for 2 hours. Broken lines indicate calculated values after Docter & Zielhuis (1967)*

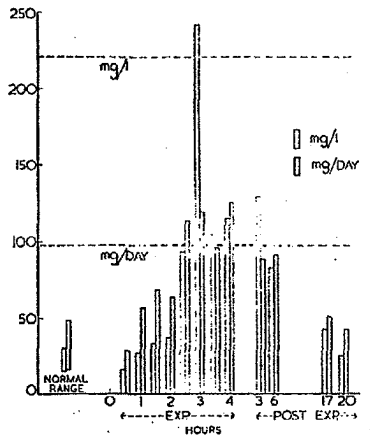

Fig 5 *Half-hourly urinary excretion of phenol during and after defined exposure to benzene vapour at a concentration of approximately 100 mg/m³ for 4 hours. Broken lines indicate calculated values after Docter & Zielhuis (1967)*

intensities. More research is needed to determine the pharmacodynamics of compounds of the nature of the toxic solvents in man, and in such studies the absorption and elimination of the parent compound and the elimination of its metabolites will be defined. For it is better to detect absorption in this fashion than to wait for pathological changes to announce industrial over-exposures.

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Dr M K Williams
(*London School of Hygiene & Tropical Medicine*)

Comparative Merits of the Tests of Lead Exposure

Possible reasons for the divergence of opinion concerning the merits of various tests of lead exposure are tradition, expense, acceptability and lack of evidence. The ideal test should have a high correlation with lead exposure, or lead poisoning, whichever is being determined; a low variability, because if the scatter is small more weight can be given to an estimation; and, for screening, a low cost because more readings can be obtained on a given budget.

The comparative merit of each test for estimating lead exposure may be calculated as the slope

of the regression line on lead-in-air concentration, divided by the standard deviation about the line. A survey has been made in an electric accumulator factory (Williams *et al.* 1968). Thirty-nine lead workers and controls whose lead absorption was fairly stable wore personal samplers every working day for two weeks to obtain estimates of their exposure. During the second week six biological tests were each estimated daily. Blood lead was found to have the greatest merit followed by urinary lead and coproporphyrin together. Urinary δ-aminolævulinic acid was of less merit, the punctate basophil count of little merit and hæmoglobin of no merit at the level of exposure studied. Urinary coproporphyrin had the greatest merit per unit cost.

Perhaps the method has other applications.

REFERENCE
Williams M K, King E & Walford J (1968) *Brit. med. J.* i, 618

Dr H Loewenthal (*London*) said that no laboratory test on its own could distinguish between excessive and early toxic absorption of lead. Even very high blood lead levels did not necessarily indicate lead poisoning, but hæmatological and biochemical tests taken together would facilitate diagnosis by the factory doctor. The wider use of the polarographic method of lead estimation and the use of the micro-method for the packed cell volume estimation would require smaller quantities of blood and this would help to allay the apprehension of the lead worker who did not object so much to the withdrawal of blood from his vein as to the amount which had to be taken if standard methods were used in the laboratory.

Dr Owen McGirr (*London Airport*) asked Dr Hunter if his Fig 1, demonstrating twenty-four-hour excretion of phenols after a relatively short inhalation of benzene, could be considered as an expression of a logarithmic relationship indicating a time-dose relationship. If so, this was perhaps comparable to biological responses to some physical exposures such as ionizing radiations and intense noise. He noted that even at twenty-four hours there remained a (small) body burden of phenols and wished to know whether successive exposures would increase the phenolic body burden.

Dr Hunter, in reply, said that after a single inhalational exposure to benzene vapour only one-third of the absorbed dose was eliminated in the form of urinary phenol. The urinary phenol fell to within the normal range within 24–36 hours. Therefore the residual burden of benzene must be metabolized very slowly and the body must retain a burden of benzene for each exposure rather than a burden of phenol. The benzene dose/phenol excretion time relationships were not known and relationships in Fig 1 were those for one subject.

Dr J R Glover (*Institute of Preventive Medicine, Cardiff*) said there appeared to be some confusion between absorption of toxic substances and poisoning by those toxic substances. The position was shown diagrammatically in Fig 1.

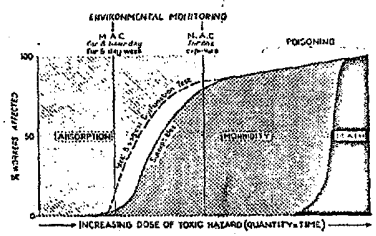

Fig 1 A model to illustrate the relationship between absorption and poisoning

Almost every hazard had a group of the population who were particularly susceptible to it and a group who were particularly resistant to it. The 'susceptible' graph was therefore S-shaped. For example, the maximum allowable concentration (MAC) of selenium was 0·1 mg Se/m³. However, a person susceptible to skin contact with selenium dioxide would show skin signs in atmospheres where selenium was so low that it could not be measured. 'Morbidity' on Fig 1 might be defined as signs and symptoms caused by the toxic hazard. This type of diagram was useful for deciding whether a test of biological dysfunction was too sensitive or too late in picking up early cases of poisoning by the toxic hazard.

Meeting June 23 1967

The meeting took the form of a visit to the Victoria Line, London Transport, which is under construction, and included Oxford Circus Station, Cobourg Street switch house, substation and control room, and Euston Station.

Meeting October 26 1967

Professor W Melville Arnott (*Queen Elizabeth Hospital, Birmingham*) delivered his Presidential Address which was entitled **Caring for the Worker.**

Meeting December 14 1967

A discussion was held on the subject of **The Early Recognition of Environmental Hazards.** The opening speakers were Dr A M Adelstein, Dr H H Pilling and Dr J C Gilson.