The Neuropsychological Effects of Solvent Exposure

Edited by:
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The proceedings of a symposium held at the London School of Hygiene and Tropical Medicine, 5th - 6th April, 1982

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The Colt Foundation

ISBN 0 9508737 0 5

Published by The Colt Foundation, New Lane, Havant, Hampshire, PO9 2LY

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SYMPOSIUM ON THE NEUROPSYCHOLOGICAL EFFECTS OF SOLVENT EXPOSURE

5th-6th April 1982

London School of Hygiene and Tropical Medicine

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PREFACE

This symposium, held in London in the spring of 1982, was set up to review critically the evidence for neuropsychological effects resulting from solvent exposure. Its objectives were to alert the industrial and scientific communities in Britain to the existence of the problem, and to establish the direction in which British, and perhaps other, research might usefully be directed. In planning the symposium, the decision was taken to invite scientists who had, in their published work, shown evidence of a critical and rigorous approach to assessing behavioural or neurological effects of industrial toxins. A number of distinct research methodologies were identified and a scientist who had carried out original work using the approach was asked to "discuss the recent advances in the understanding of the neuropsychological effects and identify areas of research in which new initiatives are needed together with the techniques which are considered most likely to achieve unambiguous results."

The first three papers presented at the meeting were concerned with the neuropathological and neurophysiological correlates of solvent exposure. Cavanagh reviewed the evidence, much of which has come from his own work, that solvent exposure may produce structural damage to the nervous system. He was able to find convincing evidence of consistent and predictable effects for only three solvents, carbon disulphide (CS_2), n-hexane and methyl butyl ketone (the last two acting through a common metabolite, 2,5 hexane-dione). Under some exceptional circumstances it appears that trichloroethylene may also produce to the cranial nerves, especially the Vth and the VIIth. Cavanagh's presentation underlined two concepts, those of the specificity of the effects of particular solvents and their reversibility, that is, recovery after the discontinuation of solvent exposure. Both were referred to repeatedly in the discussion of this and other papers.

Cavanagh concluded from his review of the neuropathological effects of solvent exposure that there was no convincing evidence of specific changes in the nervous system following exposure to solvents other than CS_2, n-hexane, methyl butyl ketone (MBK) and trichloroethylene, that the structural changes induced by these solvents appeared to be completely reversible after cessation of exposure (with the possible exception of trichloroethylene) and that it is unlikely that firm conclusions of the neuropathological effects of other solvents will be reached until we have evidence on the nature of any changes in exposed animals. Few such studies have been carried out to date. In Cavanagh's opinion, based partly on the lack of evidence of convincing clinical reports and partly on the aetiological mechanisms involved in the known solvent neuropathies, it is likely that few other solvents are capable of inducing structural damage in the nervous system. Only in the case of toluene, and perhaps styrene, is the clinical evidence sufficient to raise doubts.

The second paper was a review of the neurophysiological effects that have been detected in field studies of solvent workers. This was presented by Helen Venables who has carried out such measurements on several hundred men in the course of our own studies. The solvents convincingly shown to be capable of causing slowing in nerve conduction velocities were those which Cavanagh reported as causing structural changes, CS_2, n-hexane and MBK. Although other solvents, styrene, 1-1-1-trichloroethane, methylene chloride and paint solvents have been investigated in field studies, none has been shown to produce slowing of nerve conduction in men at work.

Otto's contribution to this part of the symposium was to review other physiological techniques that might prove useful in the toxicological assessment of workers exposed to solvents. Three clinically validated evoked potential measures are suitable for use in the field whereas others, such as event-related slow brain potentials, appear to be less practicable for use outside the

laboratory. Using the laboratory based tests, Otto has demonstrated effects associated with exposure to low levels of lead in children and it may be that the methods he describes could be used to demonstrate neurophysiological correlates of the acute effects of circulating solvents, and as such provide neurophysiological evidence of changes in central nervous system functioning not associated with structural damage.

The two papers that followed dealt with certain toxicological aspects of solvent metabolism that appear important in understanding the differences in solvent effects, particularly in the types of solvent mixtures commonly encountered in industrial use. Waldron discussed the mechanisms of the potentiating or inhibiting effects observed when certain solvent combinations (methyl ethyl ketone and MBK, for example) are encountered together. He also raised the toxicological implications of solvent exposure in association with other pharmacologically active substances - drugs and alcohol - which may be present in appreciable quanities in some workers exposed to apparently safe levels of organic solvents. The toxicology of solvent mixtures also formed the basis of Cohr's report on the substantial differences in effect found in Denmark when white spirit with a high proportion of aromatic amines was substituted by one which contained predominantly aliphatics. Some of the aliphatic molecules in white spirit, especially the long chain hydrocarbons are structurally similar to the lipophilic end of the fatty acids that form part of the membrane of the nerve cell and they seem able to alter membrane function without producing any obvious structural lesion.

The evidence reviewed to this point had been derived mainly from experimental exposure. However, the next session focussed very firmly on the source of evidence that is perhaps least scientifically convincing but most difficult to discount. The researchers present at the meeting were critical, and one or two frankly sceptical, of some of the evidence produced from scientific enquiries but most, in their clinical experience, had encountered

patients whom they felt to be suffering from a solvent induced psycho-organic syndrome. In the last paper of this session, Hernberg gave descriptions of Finnish patients, drawn from the histories of the 600 diagnosed as suffering from the condition. King, then described the neuropsychological sequelae of solvent abuse, concluded that the incidence of neurological impairment was low and affected the cerebellum rather than the cerebrum. By contrast, the criteria for diagnosis in Finland give greater weight to cerebral changes, the organic brain syndrome being characterised by subjective symptoms together with clinical neurological signs or psychological changes, or changes in the EEG or EMG. In his paper on the clinical evidence, Hernberg also reviewed some of the cross-sectional studies of exposed workers, thereby providing a background for the British work presented later in the symposium.

Axelson had been invited to review the epidemiological evidence for an excess of disabling psychiatric symptoms related to long term exposure to solvents. Two case-referent studies, from Sweden and Denmark, appear to show a risk ratio of early retirement on psychiatric grounds of approximately two for workers occupationally exposed to organic solvents in the building (Sweden) or wood working (Denmark) industries. A Danish cohort study of painters also demonstrates an apparently high risk of presenile dementia amongst workers exposed to solvents. In his review, Axelson identified those factors that might have contributed to an over-estimate of risk for the exposed groups and emphasised the need for further epidemiological studies amongst populations in which there was less possibility of bias in diagnosis of solvent workers than is now current in Scandinavia.

The clinical evidence reviewed by Hernberg and the epidemiological studies by Axelson were concerned with the possibly disabling neuropsychological effects of long term solvent exposure. The next two papers reviewed the evidence for short term changes following exposure to solvents at levels currently found in

occupational settings. The reviews concentrated largely on methodological issues, in the design of studies and in the choice of behavioural tests. Andersen reviewed the evidence derived from experimental exposure of human volunteers in a controlled climate chamber. He concluded that the very high proportion of negative findings from such studies could not necessarily be taken as evidence that exposure at those levels had no neuropsychological effects. Three issues, the level of sensitivity of the tests, the paucity of numbers of subjects and the use of healthy student volunteers rather than repeatedly exposed workers seemed likely to lead to type 2 errors, an over conservative acceptance of a null hypothesis.

These problems are largely overcome in studies, reviewed by Gamberale, of the measurement of neurobehavioural changes that may occur during the work shift amongst workers exposed to solvents. The studies reviewed by Gamberale all took place amongst workers habitually exposed to solvents (rather than student volunteers) and the numbers involved were generally greater than could easily be accommodated in an experiment using controlled exposure.

Other problems are introduced, however, in a design in which the individual levels of exposure and the nature of the work task cannot be controlled by the experimenter. The studies reviewed by Gamberale, however, have been able to give a rather convincing demonstration of the narcotic effect of a number of organic solvents, workers performing less well after exposure on measures of alertness than non-exposed men on the same shift. In his review, Gamberale provides impressive evidence that solvents have an effect on one test, simple reaction time, known to relate the physiological arousal, that is predictably and reproducibly found by different research teams in several countries and with a number of solvents.

A short presentation by Otto of a computerised assessment battery for human toxicity evaluation lead to a lively debate both on the criteria for choosing behavioural tests to evaluate short

term changes and chronic damage associated with solvent exposure and on the method of choice for administering these tests. Standardisation of administration across studies can be achieved by computer based testing with little opportunity for inter-tester bias; such an approach to testing may be unfamiliar to many workers, however, and may be alienating to those whose recent solvent exposure is associated with tiredness, irritability and lowered motivation.

The final session of the meeting broke somewhat with the format adopted previously. It began with a review of the work on the neurobehavioural effects that has been carried out in Britain, these studies being felt to be of special interest to the representatives of British industry who had been invited to attend the meeting. The session closed with contributions from three discussants who identified some of the issues particularly pertaining to their own area of expertise. Lucas (standing in for Maria Ron who was taken ill at the end of the first day) spoke on psychiatric issues. Oakes on statistical and epidemiological problems and Summerfield on some of the aspects of psychological testing. Their remarks are included in full in this report. We would conclude, however, by identifying the main issues that appear to us to be unresolved.

During the meeting it became clear that we do not have adequate evidence in a number of areas, largely related to the long term effects of solvents on the central nervous system; by contrast there is now quite good knowledge of the acute effects and of those on the peripheral nervous system.

1. The nature of the effect

   (a) Acute effect

   Organic solvents appear to have some transient or acute narcotic effects at relatively low levels. These effects are probably caused by changes in membrane function analagous to those which occur with convential anaesthetics. The extent of the effect may relate to the physical properties of the solvent, but all the common organic solvents appear capable of producing this effect to some degree.

(b) Peripheral nervous system

With regard to the peripheral nervous system, it appears established that only a small number of solvents produce effects, that these effects have a specific structural correlate and that onset is relatively rapid.

(c) Central nervous system

There is an almost complete lack of evidence for pathological change associated with long term effects on the central nervous system and indeed, the strongest evidence for long term effects comes from epidemiological studies in which ex-solvent workers are found to be suffering from an excess of psychiatric illness. The evidence for long term effects amongst people still at work is derived largely from clinical descriptions or from cross-sectional studies showing small deficits in performance on cognitive, motor or memory tests, together with minor psychiatric symptoms. The aetiology of such behavioural changes is unclear, however, and it is by no means certain how far cognitive and motor performance is affected over and above changes in mood or motivation which may affect learning or performance in the behavioural tests. It is also unclear how such changes in men still at work relate to the disabling psychiatric illness investigated in the epidemiological studies.

2. Specificity of effect

Although acute narcotic effects appear to be common to all solvents and peripheral nervous system effects to very few, there seems to be no general agreement on whether the long term effect on the central nervous system could result from all, or simply from some specific solvents, which, with the exception of CS_2, are yet to be identified.

3. Reversibility

(a) Acute effects

It is assumed that the acute narcotic effects of low doses of solvents are completely reversible in the absence of further exposure although it remains possible that the health of workers repeatedly exposed to occasional very high levels might be more vulnerable to intellectual deterioration in later years.

(b) Peripheral nervous system

As has been shown in this meeting, solvent induced changes in the peripheral nervous system recover once exposure is discontinued though complete recovery may take months to achieve.

(c) Central nervous system

We do not yet appear to have good information on the reversibility of long term effects on the central nervous system. Unlike presenile dementia, the solvent induced syndrome is thought not to progress after the man has been permanently removed from exposure and there is some anecdotal evidence that the condition may improve.

4. Dose-response

In exposure chamber studies the acute effects of solvents appear related to the atmospheric concentration and similar effects are found, at least in animal studies, for the effects on the peripheral nervous system. Even in the epidemiological studies of long term effects on the central nervous system there seems to be some debate about the nature of the dose-response relationship and there is little evidence of any dose-response relationship in cross-sectional studies of subclinical effects.

5. Special sensitivity

It may be reasonable to conclude from the experimental work that all subjects would, at some dose, suffer acute effects from solvent exposure or from changes in the peripheral nervous system where exposure is to a known neurotoxic solvent. Any central nervous system effects, however, seem to follow a different pattern with no excess of problems being found in some populations with very high exposures whereas other workers appear to have quite marked central nervous system impairment following exposure to relatively low concentrations and relatively short periods of exposure. It may be that the central nervous system of some individuals is particularly sensitive to the effects of solvents; however, insofar as these effects resemble effects found with ageing in the non-exposed population, and that the rate of ageing differs between individuals, it may be difficult to differentiate between solvent workers who are at the extreme end of the ageing distibution and those who may be specially sensitive to solvents and who would not demonstrate these changes in the absence of exposure.

6. Methodological issues

There appear to be three areas in which a concensus is lacking and which merit further discussion.

(1) Choice and administration of tests.

There appear to be (at least) two distinct hypotheses about the nature of the behavioural effects of solvent exposure, first that short term exposure at low levels causes rapid and transient depression of arousal and, second, that long term exposure may cause minor organic brain damage. The measures chosen to test these hypotheses will be different and will need to reflect the supposed effect and not simply be taken wholesale from a multi-purpose 'behavioural test battery'.

The choice of a method to administer these tests also needs care. Many of the tests originally designed for clinical use by psychologists assessing individual patients have now been adapted and are available as computer administered tests. Machine testing is highly attractive in that it allows the simultaneous testing of several subjects using a standardised procedure that can be easily reproduced by other research teams. Computer testing also has a marked advantage where 'blind' testing of exposed and non-exposed subjects at the workplace is required; solvent workers in their work clothes are readily identifiable by a human tester.

The problems with computer testing lie first in their poor acceptance to workers unused to following written instructions and unfamiliar with visual display units and keying in responses. Second, in circumstances in which this is not a problem, or where the difficulties can be overcome by pre-test periods of familiarisation, there remains a problem in interpreting the cause of any apparent deficit found amongst the workers exposed to solvents. Poor scores may reflect either a real deficit in cognitive or motor capacity, or a difference in motivation between the exposed and referent groups. Such a difference may arise from mood changes or fatigue caused by solvent exposure on the day of testing, from affective components of a sub-clinical psycho-organic syndrome or from other factors such as the possibility of compensation. Such motivational differences can be largely overcome by an experienced tester who can establish a rapport with an individual subject during a test session; the human tester may, while maintaining a standard testing procedure, minimise the contribution made by motivation to differences in scores on tests of cognitive or motor performance.

(2) The choice of referent groups in cross-sectional studies

Evidence of sub-clinical performance decrement amongst solvent workers rests largely on cross-sectional studies in which test scores of those exposed to solvents are compared with those of a referent population of non-exposed workers whose capacities are judged to have been roughly equivalent at the start of the job. The usefulness of such studies depends largely on the validity of this supposition of prior equality. Were referents from several occupational groups, requiring different skills, taken for each worker and were a distinctive and reproducible pattern of deficit found on specific types of test, this cross-sectional design might be thought to provide evidence that was sufficiently convincing to require changes in, for example, hygiene standards. Where the alternative hypothesis (that any deficit observed after exposure simply reflects pre-existing differences between the exposed and referent groups) cannot be adequately discounted, it may be a better research investment to initiate follow up studies of carefully matched pairs of new entrants to the exposed and referent groups and, by repeated testing, to identify the stage in exposure when test scores begin to diverge.

(3) Diagnostic criteria

Epidemiological studies of the long term effects of exposure have shown an excess of solvent workers amongst patients with clinically diagnosed and disabling psychiatric illness. The diagnostic categories in which the excess is found is not uniform, either within or between studies. Patients receiving compensation in Finland are spoken of as suffering from 'solvent induced psycho-organic syndrome', while in Denmark an excess is found of a 'presenile dementia' that would not however easily fit into this diagnostic category in Britain. If comparisons are to be made between findings of

research groups investigating such disabling illness in solvent workers it would be helpful to reach some agreement on definitions and diagnostic categories.

7. Standards and settlements

Some of the issues raised by evidence of the neurophysiological effect of solvents go beyond those amenable to scientific judgements, and these are perhaps best debated at forums other than that of a scientific symposium. However, two points seem to emerge from the discussions at this meeting. First, there is the question of compensation; the appropriateness of a policy of retirment and compensation seems to depend not only on the degree of certainty of the causal link between exposure and the syndrome, but also on some assessment of the extent to which those symptoms truly attributable to solvent exposure are reversible. Where reversible changes are detectable at a sub-clinical state a programme of monitoring with re-assignment to non-exposed work of particularly sensitive individuals may be more appropriate than compensation after the sympoms are well established.

Second, even if it is held that the long term health risk from occupational exposure to many of the common solvents has not been adequately substantiated (and the epidemiological evidence suggests that such a position may not be tenable) there remain the economic and social issues raised by the evidence of wide spread, if transient, changes in feelings of well being during the working day. While it may not be felt reasonable that men and women exposed to solvents should feel worse at the end of the day than their colleagues in non-exposed occupations, it must also be recognised that the economic costs of reducing exposure levels to eliminate all changes in mood state would often be extremely high. The issues involved are in many ways similar to those raised in the efforts to redesign jobs to eliminate unduly arduous or monotonous tasks; although the principle of improved working conditions can be readily agreed, the implementation of

measures to achieve this aim may, in the absence of enforcing legislation, require a marked change of atttitudes amongst all but the most enlightened (and financially secure) employers.

Finally, we must recognise that the scientific community is still a long way from being able to give to medical officers in industry or to administrators framing legislation, clear cut advice, based on neurophysiological investigations, on levels of exposure for any but the handful of solvents known to cause structural nerve damage. For while there is good evidence that transient effects result from exposure to many solvents, the conclusions from studies of long term exposure do not seem to us to be sufficiently clear to form a basis for recommending exposure levels where specific evidence of toxicity is not available for that solvent from other sources. There are, however, sufficient grounds for continued concern about the effects of long term exposure, both to individual solvents and to solvent mixtures, and we hope that one result of this meeting, and of its published proceedings, will be to contribute to the changing perceptions, both of workers and management, of the acceptability of working in unnecessarily high levels of solvent exposure.

Nicola Cherry and H.A. Waldron London, 1983

1. INTRODUCTION

K.P. Duncan

The fact that we are having a symposium on this subject is of great significance for it shows the enormous change there has been in the working environment in the last twenty or thirty years. We have moved from the classic problems of occupational medicine into a quite different area and we now have to ask ourselves far more difficult questions than some of those we used to deal with. Classically, occupational physicians dealt with clinical symptoms, with a diagnosable disease which was easily attributed and mostly easily identified; much of the detection of disease was done by astute clinicians. One thinks of Percivall Pott and scrotal cancer in the last century or of the nasal sinus cancer study which is often put down as a victory for the epidemiologist but was really a victory for the clinicians, whose awareness of an increased incidence of the disease lead to the occupational cause being attributed to wood working. Now, we are dealing with more subtle changes and we have to ask ourselves different questions.

My job is to do with government and with regulations and matters of that sort, and I wonder if it would be appropriate if I try to spell out what the administrators would be looking for from the work that researchers are doing, and that other people are pushing forward. The difficulties of the problem are large; there is a separation in time, in some cases, between the events under study, and we are dealing, not with frank clinical disease, but with biochemical or physiological changes which may or may not restore themselves. The whole issue is then confused by biological variation. Under these circumstances, how do you satisfy yourself that there is a true causal atrribution between exposure to some substance and the changes detected in the exposed population? The first question is, can an effect be detected at all, and if so, is it an objective effect or a subjective effect? If it is an objective effect, is it repeatable by different observers? Is it exposure or dose related? Does the dose relationship vary between individuals, that is, is there individual sensitivity?

So far as subjective effects are concerned, I think additional questions have to be asked; is the study blind, and are there any confounding factors? The example I think of in this connection is the work that has been done on electrical fields, where unconsciously or subconsciously subjects may be aware of some effect on the hairs or the skin so they become aware of different experimental conditions. Another important question which has to be asked is, does the effect matter? That may seem a silly question but I think we often slip into an error here because when we detect an effect we equate it with damage, and this is not necessarily the case. If the effect does matter, does it matter at the time or only much later? What is the later pathology with which you are concerned? Does the effect reverse itself or is it treatable? These considerations lead on to the next question; can a control limit be set? Can we construct a dose-response curve from which we can infer dose-effect and dose-damage points.

Having established an effect that matters (in the sense that it persists) and that it is damaging (in the sense that it remains there), is the amount of damage acceptable? Is it something about which we really need to care very much? We also ask ourselves, if that is so, is a metabolic pattern established, can ways for biological monitoring be devised? Does the metabolic pattern relate to atmospheric levels?

In the particular field we are discussing here there are additional problems. There are difficulties in measuring exposure, because we are dealing with highly volatile substances which are not only readily inhaled, but which may also be absorbed through the skin. Absorption through the skin and lung varies with exercise and effort. Thus it may be that environmental measurements give only a crude estimate of exposure, and this causes great difficulties in predicting biological events from environmental levels.

One of the difficulties for those of us trained in a more physical school is in accepting the validity of results based on questionnaires and on psychological testing. This is an attitude

that has to be faced until more objective measures, such as measurement of nerve conduction velocities, for example, can give a more revealing certainty at higher exposures. The examination of the workforce for small changes is becoming a more important aspect of occupational health and in relation to the present discussion I would like to have the answers to four questions at the end of the symposium.

First, are there repeatable objective or subjective effects which can be agreed on by experts working in the field?

Second, what is a biological significance of those effects?

Third, is there enough knowledge of the metabolism of the substance to fix control levels, both environmental and biological?

Fourth, do other agents cause the same effects or do they act synergistically?

These are the questions which our administrators are going to ask. If you can come up with detailed answers to them, then we shall be very grateful and, perhaps some of us will also be very surprised.

Discussion

Waldron: One of the difficult areas to which I hope we will address ourselves is the possibility of predicting what sort of effects will arise from different compounds. My interpretation of published work is that specific areas of central nervous system are not preferentially attacked by different volatile agents. It would be helpful to know more about the neuropathological effects of solvents so that we could determine the changes to look for in people exposed to solvents at work.

Cohr: We should be aware in these discussions, that there are two kinds of organic solvents, those that are water soluble and those that are lipid soluble and they may exert different effects.

Waldron: Is it possible to predict the neurotoxicity of solvents on the basis of their lipid solubility? Several physico-chemical properties of solvents determine their toxicology; there is, for example, the well-known relationship between boiling point (or vapour pressure) and cardio-toxicity (Clark and Tinston, 1973).

Cohr: We have some indications. We know that aliphatic hydrocarbons are more neurotoxic than aromatic hydrocarbons. We have shown that the white spirit which contains only aliphatic hydrocarbons and no naphthalene and no aromatics has the largest effect on neuropsychological tests.

One feature of the metabolism of solvents is that they may accumulate in fatty tissues and re-distribute themselves when exposure has stopped, so that exposure effectively continues even after leaving work.

Gompertz: There are, in fact, four separate classes of solvents to consider, soluble and non-soluble, and metabolised and non-metabolised.

Axelson: It is possible to order the toxicity of the various solvents either by their solubility or some other way, but in practical terms there is virtually no such thing as pure exposure in the workplace, and this limits the value of predictions based on a purely experimental approach.

Hernberg: Dr. Duncan mentioned the question of acceptability and I would like to hear some more views of this concept of acceptability. For example, it may be the case that workers experience subjective complaints, which are all reversible but nevertheless are always present so long as the exposure continues. Would that be acceptable?

Duncan: This question of acceptability is very difficult. The first decision to make is, by whom is an effect said to be acceptable? I do not think there is a simple single acceptable level of risk; that does not seem a sensible concept and I believe there is no such a thing. In this country we look at the problem in two stages. We assess the effect of a substance in as objective a manner as possible and then we look at the scale of use of this substance in industry, how it is used, how best it can be controlled in a practical sort of way. We then try to bring these two things together, and this has to be done with the people whose risk it is. In other words, is it acceptable by the people who are going to be taking the risk? It must also be borne in mind that level of acceptability will vary with social circumstances and all sorts of other factors. I think it is not for a meeting of this sort to say what is acceptable, it is for us to describe the consequence of certain actions; the decisions on acceptability have to be taken elsewhere.

Cherry: I think this notion of acceptability is something which is relevant to some of the results we find, because I think people's concept of their health, and what may affect it, may well differ between countries. For instance, some of the questionnaires that were extremely sensitive in Sweden with solvent workers exposed to high levels just do not pick up symptoms in this country. Now, either solvents do not affect the people in Britain, or they do affect them in the same way, but British workers have a different concept of health and do not expect to complain about certain symptoms; or they may have no concept that the effect on their health is important. Whatever

the reason, solvent workers in this country do not complain with anything like the same regularity as they do in Sweden.

Carter: One of the problems of separating scientific from political decisions is that any scientific uncertainties get carried over to the political arena where they cannot be debated so effectively. I hope that when we consider whether changes in psychological test results matter we can discuss how the changes relate to the effects of diurnal variation, the effects of alcohol and drug use or missing a meal. I think these are important benchmarks in judging how much importance should be attached to the effects produced by solvents.

2. SOME CLINICAL AND NEUROPATHOLOGICAL CORRELATIONS IN FOUR SOLVENT INTOXICATIONS

J.B. Cavanagh

Where the adverse effects of chemicals on the nervous system are concerned, it is only when we are in a position to make good clinicopathological correlations that we begin to set foot from the ground. Moreover, when we can advance to the next step of reproducing the condition experimentally in animals, then we can make a start to gain insight into the underlying mechanisms. It is the structural complexity of the nervous system more than anything else that makes us proceed with such caution before we can begin to make statements about causal mechanisms underlying the neurotoxicity of chemicals. In this essay on four solvents and their possible or likely effects on nervous tissue (Table 2-1), a few lessons will emerge that I hope may be valuable in making further progress.

Trichloroethylene Intoxication

Not long after its introduction as an anaesthetic, curious clinical signs of toxicity were reported (Carden, 1944; Humphrey and McClelland, 1944) in which the patients suffered marked and persistent sensory disturbances of the face, mouth and lips. Amongst the most severely affected cases were those of Buxton and Hayward (1967). These were workmen cleaning out a trichloroethylene tank. Symptoms began after about twenty-four hours with numbness and tingling of the upper lip that spread gradually to the face, forehead, upper gum and palate. After six days these symptoms were unchanged and objective sensory loss was apparent over the areas of the first and second branches of the trigeminal nerve, and in addition there was slight weakness of the facial muscles. By day eight there was ptosis, a right external rectus palsy and diplopia. Despite apparently normal fundi, the right blind spot was enlarged and there was a left central scotoma with constriction of the visual fields.

NEUROLOGICAL DISTURBANCES CAUSED BY FOUR SOLVENTS

Solvent	Proximate Toxic Substance	Structural and Functional Changes
Trichloroethylene	[Dichloroacetylene]	Trigeminal nerve senory changes Motor paralysis of V, VI, VIII, IX, X & XII cranial nerves
Carbon disulphide	[CS_2]	Psychiatric disturbances Personality disorders Peripheral neuropathy, sensory and motor (slowing of conduction)
n-Hexane, methyl n-butylketone	2,5-Hexanedione	Peripheral neuropathy, sensory and motor (slowing of conduction) Changes in visual evoked potentials
Toluene	?	Ataxia of cerebellar origin Cerebellar atrophy

TABLE 2-1

There was now evidence of weakness of the Vth motor nerve as well as facial palsy and loss of sensation in the anterior part of the tongue. By day nine one patient could not protrude the tongue or swallow solids, and he remained in this state for a long while. Even two and a half years later he had slight facial weakness and sensory disturbances in the face region, but the condition was to some extent obscured by continued litigation for compensation.

Another man, who had been as long as four hours in the tank on day two developed diplopia, day three circumoral numbness, day six facial diplegia, day eight aphonia from laryngeal paralysis and on day twelve loss of function of the hypoglossal nerve (Figure 2-1). He died after being in a respirator for some days and gross degeneration of the Vth nerve and nuclei was found in the brain as well as changes in the other cranial nerve nuclei. Unfortunately the pathology was obscured by evidence of hypoxic cell damage in the globus pallidus, red nucleus, substantia nigra and mammillary bodies.

It is generally believed now that this train of events is unlikely to be due to local entrance of the toxic chemicals in to the nerve endings in the nasopharynx for it occurs when the anaesthesia has been given by intubation. Even though we now know that substances can readily enter motor nerve endings and pass to the nerve cell bodies by axoplasmic transport mechanisms, there is no evidence in this instance of this taking place. Unfortunately experimental studies have not been made to explore this possibility. In one experiment in rats chronically exposed to dichloroacetylene, the probable toxic conversion product of trichloroethylene (Henschler et al, 1970) (Figure 2-2) in which some hind limb paralysis was said to have occurred, the animals were not studied morphologically (Siegel et al, 1971). We, therefore, have no experimental evidence about the mechanism of intoxication to guide us. All we can say is that this is a special kind of neuronal sensitivity to a toxic chemical, which is to some extent repeated by the drug stilbamidine used in the treatment of Kala-azar (Collard and Hargreaves, 1947), but the involvement of many

cranial nerve nuclei, motor as well as sensory, make this a unique intoxication. Only experimental studies can tell us more of the underlying mechanism.

Carbon disulphide

Carbon disulphide (CS_2) has long been known to affect the nervous system in several different ways. These can be divided into:-

1. functional disturbances affecting higher cerebral performance,
2. peripheral neuropathy, and
3. disturbances associated with vascular disease.

These last are not specific so far as the nervous system is concerned. The cerebral functional disturbances are relatively rapid in onset and appear likely to be related to disturbances in transmitter metabolism. As pointed out by Magistretti and Peirone (1961), many of these disturbances to higher cerebral function mimic overdosing with monamine oxidase inhibitors. Magos (1972), however, has produced evidence that dopamine-β-hydroxylase, which converts dopamine to noradrenaline, may be significantly inhibited in CS_2 intoxication and be responsible for these. Such functional disturbances, although serious and dramatic when present, are relatively rapidly reversed on removal from exposure, and produce no permanent effects. More important are the structural changes associated with the peripheral neuropathy which are slow to develop and very slow to recover.

Features of CS_2 peripheral neuropathy

The earliest symptoms are distal sensory disturbances, dysaesthesia and numbness, as well as motor weakness, tiredness and loss of reflexes. Ataxia does not seem to be an associated feature. Electrophysiological studies have shown (Vasilescu, 1972) that slowing of conduction velocity is an early warning feature and this correlates well both with animal studies and with the structural changes.

In rats chronically exposed to CS_2, Seppäläinen and Linnoila (1976) found that slowing of conduction velocity preceded any

other physical sign and was reversible if exposure was stopped. Following the earlier studies of Szendzikowski et al (1973), Cavanagh, Szendzikowski and Wronska-Nofer (unpublished findings) found that the earliest changes in nerves demonstrable in rats, before the onset of overt weakness and paresis and at a time when conduction velocity would already be expected to be slowing, were the formation of swellings within axons due to the accumulation of large amounts of neurofilaments. In teased preparations of these nerves there was pronounced swelling of the paranodes proximal to the nodes of Ranvier, with rather shrunken-looking adjacent distal paranodal regions by contrast (Figure 2-3a-d). Along any one fibre, by no means all proximal paranodes were thus affected, and their occurrence appeared to be random. The myelin overlying the swollen axon was considerably thinned (Figures 2-4 and 2-5) and might occasionally appear to be absent. The frequency of these swellings, their occurrence near nodes and the myelin thinning were considered to be sufficient to account for the slow reduction in conduction velocity and for its reversibility in experimental animals on removal from exposure.

Ultrastructurally, at this stage of evolution of the intoxication, the swelling of axons is accounted for by a striking increase in 10 nm intermediate neurofilaments. These are normal constituents of axons which, so far as we understand it at present, are made in the perikaryon and slowly (1-2 mm/day) move along the axon (Lasek and Hoffman, 1976). Their functions are unknown, but they may have structural (cytoskeleton) properties and be concerned with axonal growth. They are probably degraded in the terminal parts of the axon, and possibly elsewhere, by calcium activated proteases (Pant and Gainer, 1980).

The result of such abnormal masses of filaments is to push the other intra-axonal organelles, microtubules, mitochondria, and smooth endoplasmic reticulum, to the periphery of the fibre or into clumps among the filaments.

With increasing severity of the condition, Szendzikowski et al (1973) showed that swellings began to appear along the

internodal regions as well, and Wallerian degeneration made itself apparent. The mechanism of this last event in this particular condition has not been investigated, but if we allow ourselves to argue by analogy from the closely similar changes in hexacarbon intoxication (described later), it is probable that the filamentous masses tend to obstruct the flow of organelles and other constituents required in the day-to-day metabolism of the axon and its terminal regions. Axon degeneration is probably not a direct effect of the chemical interfering with its vital metabolic processes, but a secondary mechanical or rheological consequence of the filamentous masses obstructing axoplasmic flow through the numerous constrictions at either side of each node of Ranvier (Cavanagh, 1982).

So far attention has only been paid to peripheral nerves because they are more readily approached and studied. Our observations (Cavanagh et al, unpublished) indicate that the CNS is probably equally, if not more, affected by this process. Sections of the spinal cord and the medulla from rats with relatively mild peripheral nerve changes show very striking swelling of axons (Figure 2-5). However, very little axonal degeneration was seen, and it might be expected that, as with peripheral nerves, signs and symptoms of the CNS disorder will be expressed when either enough axonal swelling and myelin thinning occurs to block or slow axon conduction significantly, or degeneration of fibres begin to make themselves apparent. Only further study will allow us to say whether, and in what circumstances, this occurs.

Recovery from intoxication

While CS_2 intoxication, from a structural standpoint, has still to be adequately described in both the CNS and the PNS the present evidence suggests that it is similar in its basic intracellular mechanism to that of hexacarbon intoxication. Axons that do not undergo degeneration, therefore, will be expected to recover by the slow transport of the filamentous masses towards the terminals where they will probably be adequately degraded. Axons that degenerate, because the nerve cells responsible for them will be intact, will be capable of regeneration and restoration of function,

at least in the peripheral nerves. The process is likely, however, to be slow because the length of degenerated fibre, and therefore of its regeneration pathway, may often be considerable. These conclusions in general are in concordance with the clinical situation where recovery is always reported to be slow.

Hexacarbon solvents (n-hexane and MBK)

With this group of solvents we are in possession of far more information about the underlying changes and the meohanism of their occurrence, for the simple reason that experimental intoxication of laboratory animals is relatively simple (Schaumburg and Spencer, 1976); Spencer and Schaumburg, 1975: 1977). This is particularly so now that the metabolic pathways of conversion of n-hexane and methyl n-butylketone (MBK) to the proximate toxic substance, 2,5-hexanedione, have been worked out. Since both this and 2,5-hexanediol (the dialcohol) are water soluble, they can be readily given in the drinking water or by intraperitoneal injection. The need for the complex business of inhalation exposure is thus avoided.

The clinical picture in man

Unlike CS_2 intoxication, we do not see the grave disturbances to higher cerebral functions, although it is true that we have no understanding of the psychological effects of inhalation sought by the addict. The effects on peripheral nerves are, however, closely similar to those in CS_2 intoxication, and have been well described from the study of both industrial exposure and cases of addictive inhalation (Herskowitz et al, 1971; Billmeier et al, 1974; Allen et al, 1975; Korobkin et al, 1975). Both motor and sensory disturbances are found which tend to begin distally in the limbs. The sensory changes are symmetrical numbness and dysaesthesia with varying degrees of reduction in sensation. On the motor side, muscular weakness and particularly muscular wasting are striking, but ataxia is not a feature of this intoxication, although the subjects may walk with a broad based gait. More severely affected cases gradually develop a flaccid

quadriplegia, but the cranial nerves tend to be spared, except in the severest cases. Reflexes are depressed from an early stage.

Evidence of CNS disturbances is scarce, but optic atrophy has been noted, and delay in visual evoked potentials may be elicited. By electrophysiological methods it has been found that slowing of conduction velocity is an early feature in the peripheral nerves and evidence of motor denervation can be found by electromyography.

The picture is thus of a symmetrical disturbance particularly affecting longer fibres with often, but not always, a greater emphasis on motor functions. Recovery on withdrawal from exposure is unusually slow, and indeed for a while the subjects may get worse before any recovery is noted. Periods of a year or more are noted before good evidence of recovery can be found.

Pathological changes

It is now generally agreed that the essential cellular lesion is intra-axonal accumulations of 10 nm intermediate filaments, although how this comes about is a matter for debate. These filamentous accumulations in experimental animals occur in all parts of the axon (Cavanagh and Bennetts, 1981), but are most frequently found in the more distal regions. They occur in axons of all sizes but appear earliest and most abundantly in the larger fibres. Thus, they are found throughout the peripheral and central axons, and in the latter become conspicuous with time in the long ascending and descending tracts. A topographical survey in the rat brain has shown (Figure 2-6) that many central tracts are affected throughout the brain, and the extent of the axonal swellings is far in excess of that which would be expected from the functional disturbances which can only be appreciated in the limbs. Weakness and flaccid paresis with muscular wasting are really the only appreciable changes.

This lack of correlation between structural and functional changes has been shown (Cavanagh, 1982) to be almost certainly due to the filamentous masses only secondarily producing disturbances in impulse conduction in axons, either by thinning of the paranodal myelin and disorganising the nodes of Ranvier as the axon is

expanded, or by later producing Wallerian degeneration of axons from obstruction to the normal passage of essential materials along the axons. Such a concept of the course of events accords with the early slowing of conduction velocity, its relatively rapid return to normality on recovery and the minor functional changes in the CNS where, in general, axons are smaller, have thinner myelin sheaths and have wider nodes of Ranvier that more readily allow the filamentous masses to slip through.

Mechanism of neurofilamentous accumulations within axons

Filamentous accumulations seem to be the essential pathological change both in hexacarbon and in CS_2 neuropathy. Studies in animals have shown that n-hexane and MBK are both converted to 2,5-hexanedione whereas non-toxic compounds such as methylethylketone (MEK) and methyl isobutylketone (MiBK) are not handled by the liver in the same way (Couri et al, 1976; Di Vincenzo et al, 1976). The 2,5-hexanedione, moreover, seems to be the proximate toxic substance and can produce the specific changes in cultures of nervous tissue (Veronesi et al, 1980).

The mechanism of this is in debate. One suggestion is that there may be impairment of energy-producing mechanisms due to inhibition of the glycolytic pathway (Spencer et al, 1979). More persuasive is the suggestion (Graham, 1980) that the diketone produces crosslinking of neurofilamentous (and perhaps other) proteins by forming Schiff bases with amino groups. This could explain the relative inability of the filaments to slip through constrictions at nodes of Ranvier and thus to accumulate in the way that they do. The same mechanism is likely also to occur with CS_2 because of the closely similar sequence of cellular pathological events, but this has not yet been shown. CS_2 also has an affinity for -SH groups and has been shown to be able to inhibit a wide range of -SH dependent enzymes for this reason. Thus there are many chemical similarities between these two substances which help to explain their closely similar pathological basis.

Toluene and other possibly toxic solvents

The demonstration of a precise intracellular mechanism for the toxicity of n-hexane and MBK in no way allows us to argue by analogy to other putatively toxic solvents, even though there are suggestions of a marked effect on the CNS from reports in the literature.

Evidence of neurotoxicity from solvent mixtures containing little or no n-hexane

Sporadic cases of intoxication from the chronic inhalation of mixtures usually containing toluene in varying proportions have been reported (Table 2-2). Most often these cases have shown clinical evidence of cerebellar disturbances with or without signs indicating involvement of cerebral centres as well. The clinical evidence of cerebellar damage appears to be good in the reports of Grabski (1961), case two of Boor and Hurtig (1977), Escobar and Aruffo (1980) and of Malm and Lying-Tunnell (1980). That of Escobar and Aruffo (1980) showed marked Purkinje cell loss at post mortem examination as well as atrophic changes in the cerebral regions, but there were also swollen axons in the spinal cord and slowing of conduction velocity (30.5 m/sec vs 49-55 m/sec normal) found during life. It was suggested, therefore, that he also had the changes of hexacarbon intoxication. While the solvents inhaled probably for the most part contained no n-hexane, because of the marked variability in the formulation of the cheaper agents used, the chronic absorption of n-hexane in addition to the other substances cannot be ruled out in this case (Escobar, personal communication).

The case of Escobar and Aruffo is the only one with post mortem evidence of degenerative changes. In the case of Knox and Nelson (1966), evidence of cortical atrophy was presented by air encephalography, but cerebellar atrophy was reported to be absent. Unfortunately we have no objective information about the cerebellum of the cases of Grabski (1961) and of Boor and Hurtig (1977) although the clinical evidence is strongly in favour of degeneration having occurred and recovery of function did not take place in

REPORTS OF PROBABLE OR ACTUAL PATHOLOGY WITH LITTLE OR NO HEXANE IN SOLVENT

Author	Clinical Signs	Investigation	Pathology	Analysis of Solvent
Grabski (1961)	Classical cerebellar signs	No	Not examined	'99% toluene'
Satran & Dodson (1963)	Typical cerebellar signs	AEG-negative EEG-non-specific	Not examined	'Toluene'
Knox & Nelson (1966)	Ataxia, tremor Babinski +	AEG-atrophy EEG-diffuse slowing	Not examined	?
Prockop et al (1974)	Distal weakness & sensory loss	EEG-normal slow conduction	Biopsy - filamentous Masses in axons (1976)	Toluene - 3.9% *n*-Hexane - 0.5%
Oh & Kim (1976)	Distal weakness & sensory loss	Slow conduction	Not examined	99% Toluene No n-hexane
Boor & Hurtig (1977)	1. Opticians-ataxia & dysarthria	No	Not examined	99% Toluene
	2. Huffer-ataxia dysarthria, clonus, titubation, Babinski +	No	Not examined	99% Toluene
Sahenk et al (1978)	Distal weakness & sensory loss	Slow conduction	Biopsy - myelin & axon degeneration No filaments	N_2O cartridge containg 23 solvents No n-hexane
Escobar & Aruffo (1980)	Mental changes, Ataxia, Babinski +	CAT scan - atrophy Slow conduction	PM - cerebral, cerebellar atrophy Filaments in swollen CNS & PNS axons	Toiluene 40% Probably no *n*-hexane
Malm & Lying-Tunnell (1980)	Ataxia, dysarthria, titubation, Babinski +	No	Not examined	Toluene

TABLE 2-2

either instance. However, the case of Malm and Lying-Tunnell (1980), who seemed also to have clear cut severe cerebellar signs as well as positive Babinski responses, recovered over the subsequent eight months without residual sequelae. Unfortunately, no objective investigations were done to confirm the presence of structural changes.

While there seems, therefore, to be suggestive evidence that other solvents may produce severe degenerative changes in the CNS, the picture is complicated by reports of the occurrence also of peripheral neuropathy without cerebral or cerebellar changes in circumstances either where intake of n-hexane was minimal (Prockop et al, 1974) or was apparently absent (Oh and Kim, 1976; Sahenk et al, 1978). The cases of Prockop et al, (1974) had all the clinical hall-marks of a hexacarbon neuropathy, and the one case that came to postmortem examination showed filamentous masses within axons. The solvent mixtures used, however, either contained no n-hexane (the "good stuff") or only 0.5% n-hexane (the "bad stuff"), a concentration that is markedly less than is usually found with huffer's or glue sniffer's neuropathy reported by Gonzalez and Downey (1972) (80% n-hexane), Goto et al, (1974) (18-28%), Korobkin et al, (1975) (27%) and Takeuchi et al, (1975) (12.5%). Toluene was also present in all these reported mixtures and in the cases of Prockop et al it varied from 47% to 3.9%. In the report of Oh and Kim (1976), typical clinical symptoms of hexacarbon neuropathy were again described but the solvents used for huffing contained either MEK, MiBK, acetone and toluene or an acetone, methanol and toluene mixture. This tempts one to ask either whether the analyses were faulty or whether these other solvents might also be capable of cross-linking neurofilaments. This single case does cause one to suspend judgement as to whether only n-hexane metabolites cause this type of lesion.

The third report is that of Sahenk et al (1978) in which neuropathy occurred after addiction to nitrous oxide inhalation from a whipped cream cannister. This case is unique, however, not only in showing that the patient probably inhaled twenty-three

different types of organic chemicals, but also that the nerve biopsy apparently showed both a demyelinating Schwann cell lesion as well as an axonal degeneration; no filamentous axonal accumulations were seen.

Conclusions

There is some clinical evidence that solvents, other than CS_2, n-hexane and MBK, may be responsible for serious damage to CNS structures. The cerebellum appears to be particularly at risk, but damage to the cerebrum and to other brain centres occurs, apparently, almost as often. These are only clinical case reports, however, and they are in need of firm objective evidence to support this suggestion before we can definitely incriminate solvent mixtures in this way. Moreover, until careful pathological examination of other cases is made, and similar changes can be produced in experimental animals, we are not going to make any headway in either identifying the causal agent or understanding the mechanism of tissue damage. From the distribution of the assumed lesions it is highly unlikely that the mechanism of cerebellar and cerebral damage is going to be anything like that which occurs in hexacarbon or CS_2 intoxication, although it is possible that some of these agents may enhance the toxicity of the low doses of n-hexane as is known to occur between MEK and MBK. This could be the interpretation of the cases of Prockop et al, (1974). Until every effort is made to induce these changes in laboratory animals, little progress in our understanding of the situation is likely to be made.

Acknowledgements

I would like to thank the Wellcome Trust for supporting our work on the mechanism of nerve lesions in hexacarbon intoxication.

Discussion

Goffe: Is there any experimental evidence that toluene has a neuropathological effect?

Cavanagh: There have been no satisfactory animal experiments using toluene. Some experiments have been carried out, but either the neuropathological changes have not been looked at adequately from the methodological standpoint, or they have not been looked at at all. One problem is that the brain has to be examined in a rather specialised way, using special fixation and stains, otherwise investigators who are inexperienced in this field will miss changes. I suspect that if we use behavioural techniques for studying animals and take samples from these animal groups at different times we may ultimately come across a good correlation between what we see morphologically and what we see behaviourally. I am supported in that thought because currently I am concerned with a study where there has been a lot of behavioural work on animals intoxicated with carbon disulphide and we are now killing off some of the animals after six months. In the higher dose group, where behavioural changes are starting to appear, I am beginning to have suggestions of swollen axons and so forth in the retino-tectal and other pathways. The changes are minimal but one would like to see more of this kind of collaborative work because how else are we going to judge the efficiency of these behavioural tests in such a structured organ as the brain? In view of the cases of cerebral atrophy with CAT scan changes such as dilated ventricles and widened sulci, I think there must be some kind of morphological change going on which would be picked up.

Otto: My colleague, in reviewing the literature on toluene came to the conclusion that, short of killing the individual, there is no evidence of irreversible changes from toluene exposure (Benignus, 1981).

Cavanagh: Most of the reported cases that I have listed here (Table 2) have been irreversible in that a year or so later, they still have been clinically the same. There was one case that I did not have time to discuss in detail. That was the Swedish case (Malm and Lying-Tunnell, 1980) of a woman with marked cerebellar and other signs who became normal again after eight months. Since no detailed clinical investigations are described, it is difficult to know what was happening, however. This case emphasises the need always to do CAT scans in any investigation of supposed cerebral, or cerebellar damage.

Wilkinson: In your table of the effects of CS_2 on rabbits and their recovery there-from, I thought that in fact, they seem to be recovering to normal but asymptoting below that level.

Cavanagh: Perhaps our Finnish colleague here might comment on that because this was from Seppäläinen's laboratory and I do not know how long the experiment went on for. I would think, from what we know of the structural changes, they would return entirely to normal.

Hernberg: Eight of the ten animals were killed, but the two that were followed up were followed up for long enough, I think.

Cavanagh: The only problem would be if there was any substantial Wallerian degeneration, that is if the axons actually decayed, then the speed of regeneration would be impaired because there would still be a blockage in the flow of important materials required for regeneration within those axons. We have been finding quite marked slowing of regeneration in recent studies (Simonati, Rizzato and Cavanagh, unpublished).

Hernberg: We have seen recovery in some patients with carbon disulphide poisoning after a couple of years.

Goffe: Were the cases of toluene neuropathy that you described thought to be exposures to toluene only, or to a mixture of solvents?

Cavanagh: Most were supposed to have been exposed to pure toluene as far as I can make out from the descriptions. There were not many analyses carried out in fact; the patients reported that they bought 99% toluene, so that it is not confirmed.

Goffe: Apart from anything else, until very recently commercially available toluene has always been contaminated with traces of benzene.

Cavanagh: I still do not understand those cases of peripheral neuropathy, where there was virtually no n-hexane in the material, unless there is something else that might be having the same effect as n-hexane.

Cherry: Is there any evidence that you would accept that suggests that any solvents, other than those you have already mentioned, are neuropathic?

Cavanagh: Styrene appears to produce neuropathy but again the evidence is not all that good yet.

3. SOLVENT - INDUCED PERIPHERAL NEUROPATHY IN MAN

Helen Venables

In this paper, I shall briefly review the evidence that some organic solvents cause peripheral neuropathy in man. I shall first consider three solvents which have been clearly shown to produce pathological changes in the peripheral nervous system. These are carbon disulphide (CS_2) n-hexane and methyl n-butyl ketone (MBK). Secondly, I shall discuss solvents for which the evidence of their neurotoxicity in man is equivocal.

Carbon Disulphide

During the second half of the nineteenth century, CS_2 was used in the cold vulcanisation of rubber. A physician in Paris, August Delpech, recorded numerous cases of CS_2 poisoning in the 1850s and 60s. The toxic syndrome was marked by insomnia and nightmares, extreme irritability, fatigue and loss of libido. This pattern of intoxication was observed by Braceland in America in the 1940s, who also noted memory defects and hallucinations in some of his patients. Outbreaks of CS_2 poisoning were reported all over Europe during the Second World War when workers in the viscose rayon industry were exposed to high levels of the solvent for long hours in poorly ventilated factories. Vigliani examined 100 men suffering from CS_2 poisoning in 1940 and 1941; he identified polyneuropathy in 88% of his cases, the legs being generally affected more than the arms. Other common symptoms were gastric disturbances, vertigo and headaches and sexual weakness. A number of these men were examined five years later and only 25% showed signs of improvement or recovery. In Milan, Vigliani observed that the polyneuropathy in another group of CS_2 workers gradually developed into a diffuse vascular encephelopathy, leading to severe mental deterioration. One of his patients is described below:

"Case 28 - Gro. L. aged 55 had worked at Plant C as a spinner for 2 years and as a rayon bobbin washer for 13 years. From 1947 he had heaviness in his

legs with progressive difficulty in walking. He left work in May, 1952 and was admitted to hospital in 1952 with diffuse encephelopathy with symptoms of loss of power on the right side, mental deterioration and dysarthria B.P. was 160/90 mm Hg. Disability was 60%."

In 1972 and 1974, Seppäläinen and her colleagues carried out studies on viscose-rayon workers in Finland. In the first study, 36 men with diagnosed CS_2 poisoning were examined; compared with a control group of paper mill workers, they complained of more symptoms of the kind reported by earlier investigators, namely fatigue, insomnia, headaches and paraesthesiae. Nerve conduction velocity (NCV) and electromyograph (EMG) recordings were made and most of the cases had one or more abnormal measurements. In the second study, 118 men who had been exposed to CS_2 for between 1 and 27 years were studied; 52 of these men had left the viscose-rayon industry for an interval varying between 1 and 15 years. Compared with a group of 100 paper mill workers, the exposed men had slower motor conduction velocity in the legs, longer distal latencies in the median and ulnar nerves in the arm and slower conduction velocity of the slow conducting fibres of the ulnar and deep peroneal nerves. The conduction velocity measurements of the 53 men who had been removed from exposure did not differ from those men who were being currently exposed, suggesting a degree of irreversibility of the pathological changes caused by CS_2.

Methyl n-butyl Ketone and n-hexane

MBK and n-hexane produce a similar pattern of polyneuropathy characterised by a symmetrical stocking-and-glove sensory impairment, weight loss, muscular weakness and paralysis ascending from the distal to the more proximal muscles. The disease progresses after the patient is removed from exposure, but then function returns to normal over several months. Outbreaks of polyneuropathy have been caused by occupational exposure to n-hexane and MBK and n-hexane neuropathy has been observed in glue-sniffers who inhaled a thinner containing this solvent.

Yamamura (1969) reported an outbreak of polyneuropathy among workers engaged in sandal and slipper manufacture in small cottage industries in Japan. Several cases of tetraplegia appeared at a hospital in Nagoya, all of whom had been in contact with an adhesive containing n-hexane (70%), toluene and other constituents. A questionnaire was circulated to 1662 workers to screen for signs of polyneuropathy; 296 people were given a detailed examination and 93 were found to have polyneuropathy. Forty-four of these patients were given NCV and EMG tests; in the arm, 50% and 36% had abnormal MCV of the median and ulnar nerves respectively; in the leg, 70% and 48% had abnormal MCVs of the peroneal and tibial nerves respectively. The number of abnormal MCV and EMG recordings in a particular patient correlated well with the clinical severity of the disease.

An outbreak of polyneuropathy attributed to MBK was detected by Allen et al (1973) in a similar way to the outbreak in Nagoya; several cases of polyneuropathy appeared in a hospital in Ohio, all employees at the same fabric coating and printing plant. Over one thousand employees at the plant were investigated; 86 had polyneuropathy of differing severity. In December 1972, MBK had replaced methyl iso butyl ketone (MiBK) in ink thinners and cleaners; the main constituent of which was methyl ethyl ketone (MEK). The first cases of neuropathy appeared in June 1973 and the severity of the disease was linked to the level of exposure to the solvents. The temporal course of the outbreak, after the introduction of MBK into the thinners and cleaning fluids, together with the association between exposure and severity of the disease pointed strongly to MBK as the causative agent. A synergistic effect with MEK, however, could not be ruled out. A subsequent study of rats experimentally exposed to MBK, MEK and an MBK:MEK mixture (ratio 1:5) by Saida et al, (1976) showed that MEK alone had no neurotoxic effect, but caused a marked potentiation of the peripheral neuropathy caused by MBK.

Altenkirch (1977) reported 18 cases of glue-sniffers with polyneuropathy; weakening of the leg muscles progressed to

paralysis in some patients, 7 of whom were tetraplegic at the height of their illness. All 18 patients sniffed the same thinner. Two months before the appearance of the first cases the composition of the product had been changed by the manufacturers, MEK being added and the percentage composition of the other constituents (including n-hexane). Biopsy of the sural nerve revealed morphological changes identical with those commonly found in glue sniffer neuropathy (see Towfighi et al, 1976) namely densification of cytoplasm within the axon, clumping of neurofilaments and retraction of the myelin sheath. MEK is not known to have a neurotoxic effect, but can act synergistically with MBK (see above); the authors concluded that MEK induced n-hexane neuropathy in this group of sniffers.

Other Solvent Neuropathies

A number of other solvents have been investigated for toxic effects on the peripheral nervous system. Comparisons between a group of exposed workers and age-matched controls have sometimes revealed small differences in NCV measurements with the exposed workers having slower NCVs than the controls; the effects are minor, compared with those induced by CS_2, n-hexane and MBK, however.

Seppäläinen amd Harkonen (1976) found no differences in motor or sensory conduction in 96 laminators exposed to styrene for a mean duration of 5 years compared with a control group of 30 non-exposed men. Rosen et al, (1978) on the other hand examined 33 workers who had been exposed to either high (above 50 ppm), medium (50 ppm) or low levels (below 50 ppm) of styrene for 1 to 21 years, and found that they had lower amplitude and longer duration of the sensory action potential of the median and ulnar nerves compared with 6 controls. There was no consistent relationship between these measurements and level of exposure, however.

Maroni (1977) investigated 21 women who had been exposed to 110-990 ppm of 1-1-1-trichloroethane for a mean of 6.7 years. There was no difference in MCV and conduction velocity of the

slow fibres (CVSF) of the ulnar and deep peroneal nerves between three groups with differing levels of exposure and a control group. Cherry et al (1981) found no difference between 29 men exposed to methylene chloride for a mean of 13 years and age-matched controls on MCV measurements of the ulnar and median nerves. The same authors found that 59 men exposed to over 100 ppm of toluene for a mean of 9 years showed no slowing of motor and sensory conduction velocity in the median and ulnar nerves compared with age-matched controls. Knave (1976) found that jet fuel vapours at levels of 500-3,000 ppm did not lead to any slowing of MCV in the ulnar and median nerves and the CVSF of the ulnar nerve.

Considering mixed exposure to solvents, Elofsson et al (1980) and Seppäläinen et al (1978) found minor differences on a number of NCV measurements between men (car painters) exposed to low levels of xylene, toluene and white spirit and non-exposed controls. Fagius and Gronquist (1978) found that exposure to a mixture of MEK (180 ppm) and trichloroethylene (30 ppm) in a steelworks led to complaints indicative of polyneuropathy. Forty-two exposed workers were examined together with 42 referents, matched for age, sex and duration of employment, from another section of the plant, where there was no exposure to solvents. In the exposed group there was one plausible and two suspected cases of neuropathy; none was found in the referent group. NCV measurements showed no differences between the groups, but the exposed workers had a significantly higher vibration sense threshold than the non-exposed men.

Conclusion

Severe cases of polyneuropathy have been reported after exposure to CS_2, n-hexane and MBK. Small changes in NCV measurements have been found in some groups of workers exposed to other solvents. The significance of these minor impairments is not fully understood, some of the studies suffering from methodological difficulties, particularly in the choice of control group. Carefully conducted studies are needed to establish with reasonable certainty that most organic solvents are unlikely to cause peripheral neuropathy in man.

Discussion

Waldron: Is there any evidence for peripheral neuropathy in people industrially exposed to trichloroethylene?

Venables: There is one study which found neurological signs in exposed men together with various non-specific symptoms like fatigue (Grandjean, 1955). I do not know a study in which nerve conduction velocities have been measured in a group of workers exposed only to trichloroethylene.

Cavanagh: With trichloroethylene you would not expect to get a peripheral neuropathy in the limbs. This substance produces these curious cranial nerves changes which seem to be very specific.

Venables: There is a case of another metal degreaser who was exposed to trichloroethylene for six weeks. Initially, he developed some of the symptoms which accompany other kinds of solvent poisoning, such as weight loss and vertigo, before developing neuropathy of the trigeminal nerves (Mitchell and Parson-Smith, 1969). Feldman et al (1970) reported the case history of a patient with trichloroethylene poisoning who had abnormal slowing of distal sensory conduction in the ulnar nerve; this slowing reversed after several weeks.

Axelson: I wonder if you could comment on the normal values for conduction velocities. There are differences between the norms quoted by various Swedish laboratories. In some of the more rigorous studies, there have been special comparison groups, but the neurophysiologists in Sweden do not always seem to have adequate norms for routine purposes.

Venables: There is one problem I have had in looking at the literature; in some of the papers no normal values were given even though the authors reported abnormal values. In our laboratory we have now built a pool of normal data and we realise that it is important to match carefully on, for example, age. In our analyses we

look to see how many people fall, say two standard deviations away from the mean, but it is very difficult to know where to set the limit.

Jamie: Are these data that you have actually developed yourself or that you have collated from other people's work?

Venables: These are values from people we have tested ourselves. We have data from about 150 people who are not exposed to any neurotoxic substances (Appendix below).

Waldron: In these neurophysiological studies, careful matching is essential. We have found changes in nerve conduction velocity with age and with skin temperature. If the skin temperature is below 30° Centigrade there is a big fall in nerve conduction velocity.

Carter: How reproducible are nerve conduction studies in the same individual? How many of these studies have reported sequential values in the same group of people?

Venables: We have carried out small studies in our laboratory to see how reproducible these measurements are, and the answer is that they are surprisingly constant although you do have to take special care in the measurement. In most of the studies in the literature only one set of measurements has been taken.

Gamberale: We have found a correlation of 0.4 between nerve conduction velocity and reaction time in a group of 140 workers exposed to toluene. We thought that reaction time was a measure of central functions so we do not know what this correlation means.

Cherry: We have also found a small correlation between sensory nerve conduction velocity and reaction time in toluene workers but whether it is chance or not, I do not know.

APPENDIX

Normal Values for Use in Neurophysiological Studies of Male Manual Workers

Helen Venables and H.A. Waldron

Summary of procedures used to obtain nerve conduction velocity measurements.

The motor conduction velocity of the ulnar and median nerves along the forearm was measured by stimulating the nerves at the wrist and the elbow and recording the action potential with surface electrodes over the hypothenar and thenar muscles respectively. To measure sensory conduction velocity, the ulnar and median nerves were stimulated antidromically at the wrist and the sensory nerve action potentials recorded with ring electrodes on the fifth and middle fingers respectively. Our normal values are shown in the following tables.

ULNAR NERVE

		Age (Years)				
		<35	35-44	45-54	>55	Total
Distal latency	(ms)					
	$\bar{x}$	2.9	2.8	3.0	3.0	2.9
	SD	0.7	0.5	0.6	0.4	0.6
	n	53	56	40	27	176
Motor conduction velocity	(ms^{-1})					
	$\bar{x}$	62.0	59.4	56.6	57.5	59.3
	SD	6.7	5.8	6.3	6.6	6.6
	n	52	55	38	27	172
Amplitude of action potential	(mV)					
	$\bar{x}$	8.3	9.3	8.0	7.1	8.4
	SD	4.2	4.1	4.1	4.0	4.1
	n	45	55	40	27	167
Sensory conduction velocity	(ms^{-1})					
	$\bar{x}$	39.1	39.0	35.7	37.0	37.9
	SD	5.4	4.9	5.0	4.9	5.2
	n	34	31	26	18	109

MEDIAN NERVE

		Age (Years)				
		<35	35-44	45-54	>55	Total
Distal latency	(ms)					
	$\bar{x}$	3.4	3.4	3.5	3.5	3.4
	SD	0.6	0.4	0.5	0.5	0.5
	n	47	54	40	26	167
Motor conduction velocity	(ms^{-1})					
	$\bar{x}$	61.1	58.5	55.0	54.2	57.7
	SD	5.7	5.1	4.9	5.5	5.9
	n	46	53	39	26	164
Amplitude of action potential	(mV)					
	$\bar{x}$	8.7	8.5	9.2	6.9	8.5
	SD	3.2	4.0	4.2	3.5	4.0
	n	42	54	40	25	161
Sensory conduction velocity	(ms^{-1})					
	$\bar{x}$	39.9	39.7	37.5	37.3	38.9
	SD	5.6	4.6	4.7	4.7	5.0
	n	31	29	27	18	105

4. EVENT-RELATED BRAIN POTENTIALS: AN ALTERNATIVE METHODOLOGY FOR NEUROTOXICOLOGICAL RESEARCH

D. Otto

One of the problems encountered in studies of glue sniffing, and other types of solvent poisoning is addiction. This problem also afflicts researchers who tend to become addicted to a particular methodology. This paper will review some alternatives to the behavioural methods to which many of us have become addicted. These alternatives include sensory evoked potentials and event-related slow potentials of the brain. Evoked potentials are sensitive, clinically proven, indices of sensory deficits, while event-related slow potentials are sensitive, albeit experimental, indices of cognitive dysfunction. Evidence is accumulating that evoked and slow potential measures may also be sensitive indices of neurotoxic effect (Otto, 1977; 1982a; 1982b; Otto and Reiter, 1978).

There are three types of clinically validated evoked potential measures that have a straightforward application to neurotoxicity testing. The first is the brainstem auditory evoked potential (BAEP), one of the few evoked potential phenomena for which the neural origins have been relatively well established (see review by Rowe, 1981). A typical BAEP is illustrated in Figure 4-1. The first wave is generated peripherally in the acoustic nerve, the second from the region of the cochlear nucleus, the third is associated with the superior olivary complex, the fourth with the lateral lemniscus, and the fifth with the inferior colliculus. The correlation between anatomy and phenomenology is sufficiently good that the neurologist can use the BAEP to assist in localising lesions in the auditory pathway and in diagnosing nonspecific demyelinating diseases such as multiple sclerosis (Starr, 1977). Since neurotoxicants tend to produce symmetrical, diffuse effects on CNS function (Schaumburg et al, 1981) similar to multiple sclerosis, BAEPs should provide a sensitive index of neurotoxicity, particularly in the case of chemicals that produce demyelinating effects.

Several other features of the BAEP suggest its utility in toxicity testing. First, the BAEP is not affected by changes in attention. As long as the auditory pathway is intact, anaesthesia does not alter BAEP latencies (Starr, 1977). Secondly, the measure is immune to cultural bias since no verbal mediation is required. In addition, BAEPs are simple to record and the latency measures are easy to make and interpret. Central conduction time in the auditory pathway can be determined by subtracting the latency of wave I (acoustic nerve) from wave V (region of the inferior colliculus).

The second measure that I would add to a neurotoxicity test battery is the pattern reversal evoked potential (PREP). In this test, dark and light squares of a checkerboard pattern are reversed repetitively on a video display. This measure has been found to be more effective than the traditional flash visual evoked response in the diagnosis of multiple sclerosis (Halliday et al, 1973). The flash evoked potential has been used widely for toxicity testing in animal models (cf. Fox et al, 1977; Dyer et al, 1979; Cooper et al, 1980). For many substances, it seems to be a useful measure. In view of the lack of sensitivity in the clinical population of the flash evoked response, the PREP appears to be a better candidate for human neurotoxicity testing. Several Institutes of Occupational Medicine (Baltimore, Helsinki, Stockholm) have begun to use the PREP in the neurobehavioural assessment of workers, but no definitive data from these studies are yet available (see Elofsson et al, 1980).

The two measures described above have other characteristics that make them useful for neurotoxicity testing purposes. Both the BAEP (Hecox and Galambos, 1974) and PREP (Sokol and Jones, 1979) reach mature latency values by 18 months of age and remain relatively constant throughtout adult life, although there may be a slight slowing in latencies in the elderly. In general, these measures are very robust and very reliable. PREP waveforms elicited by stimulating the left and right eyes of a patient with multiple sclerosis are shown in Figure 4-2. The left-right imbalance, indexed by a differential latency of less than 14 msecs in the

P100 component, is clinically abnormal and, in this case, diagnostic of multiple sclerosis (Stockard et al, 1979).

The third electrophysiological measure that I would suggest using in a neurotoxicity test battery is the somatosensory evoked potential (SEP). Anatomically the somatosensory system is ideal for human neurotoxicity testing because the long peripheral nerves are accessible for measurement at many points along the sensory pathway. By stimulating a distal point in the pathway, both peripheral and central nerve conduction measures can be obtained simultaneously as shown in Figure 4-3. Peripheral nerve conduction velocity is determined by measuring between two points on the peripheral nerve. Central conduction time is calculated by subtracting the arrival time of the afferent volley at the dorsal column nucleus (N14 latency) from the arrival time in the postcentral gyrus (N20 latency). This method can be used in neurotoxicological assessment to determine if a deficit is peripheral or central (cf. Eisen and Odusote, 1980). Other techniques have been developed to assess neurological disorders in the spinal cord, brainstem and thalamus (Noel and Desmedt, 1980).

Few attempts have been made to apply SEPs in human neorotoxicity testing. Seppäläinen (1978) reported preliminary evidence that the scalp-recorded SEP was more a sensitive measure of subclinical neuropathy than peripheral nerve conduction in lead-exposed workers. Groll-Knapp et al (1978) compared the effects of 100 ppm (5.5% COHb) and 200 ppm (9.7% COHb) CO exposure on auditory, visual and somatosensory evoked potentials. SEP amplitude was significantly reduced at both exposure levels, while auditory and visual EPs were unchanged. Zappoli et al (1978), on the other hand, did not find the SEP useful in diagnosing toxic polyneuropathy of workers exposed to industrial adhesive solvents.

The three measures described above are clinically validated. There are other electrophysiological measures with possible applications in toxicological research that must be considered experimental because the tests have not been standardised and population norms are not available. I refer to event-related

slow brain potentials (ERSP). Sensory evoked potentials measure the integrity of sensory pathways, but provide no information on cortical integration. By contrast, ERSPs are usually recorded in the context of a behavioural task and thus reflect the integration of sensory input and motor output. For example, the subject may be presented with a single digit once per second and asked to press a button each time he detects a run of three odd or three even numbers. An example of ERSPs elicited in this type of continuous performance task is shown in Figure 4-4. The solid line represents correct rejection trials where the first two digits in the string were the same, but the third digit differed (e.g. 3-3-8). In these trials the subject correctly refrained from pressing the button. Following the third stimulus a component (called the P300 wave) appeared in the trace indicating that a correct no-response decision had been made. The dashed line represents a set of miss trials, where the individual failed to detect a target string of three identical digits. In this trace, the P300 component was absent. Note that the subject refrained from button pressing in both sets of trials, but the P300 wave occurred only when a correct no-response decision was made. The P300 wave thus constitutes a robust, easily recordable index of information processing in the brain, a convenient noninvasive measure of cognitive function.

P300 amplitude and latency have been studied extensively by psycho-physiologists and related to a variety of cognitive functions including selective attention, response set, decision-making, signal detection, orienting, and uncertainty (cf. Tueting, 1978). As yet, however, the clinical relevance of this waveform remains to be demonstrated in a convincing manner. The lack of knowledge of the neuroanatomical, neuro-physiological, and neurochemical substrates of the P300 limit clinical applications. Otto et al (1978) failed to find any relationship between P300 amplitude and carboxyhaemoglobin levels in young adults, but no systematic effort has been made to explore the utility of the P300 in neurotoxicology.

Another extensively studied ERSP is the contingent negative variation (CNV) first described by Walter et al (1964). CNV is a slow negative shift in EEG baseline that occurs between the warning and imperative stimuli in a fixed foreperiod reaction time task. The CNV has also been related to a host of psychological variables including expectancy, motor preparation, attention/arousal, and concentration. Groll-Knapp et al (1972) reported that CNV amplitude and vigilance performance varied inversely with carbon monoxide exposure levels, although they were later unable to replicate earlier findings (Groll-Knapp et al, 1978). Otto et al (1978) reported a paradoxical increase in CNV amplitude in subjects exposed to 100 ppm CO, but a decrease in subjects exposed to 200 ppm CO. Zappoli et al (1978) did not observe any effects of adhesive solvent exposure on CNV amplitude in shoe workers, despite EEG abnormalities indicative of diffuse brain damage in all subjects.

The most encouraging evidence of the potential utility of ERSPs in neurotoxicity testing derives from recent studies of slow cortical potentials in children with elevated body lead burden (Otto et al, 1981; 1982). A linear relationship between slow wave (SW) voltage and blood lead (PbB) level was observed in young children during sensory conditioning. This effect was observed across a range of 6-55 µg/dl with no evidence of any threshold effect level. The only other biological measure previously shown to be affected at such low PbB levels is delta-aminolaevulinic acid dehydratase (Hernberg et al, 1970). A similar linear relationship of SW voltage and PbB levels was observed in a subset of the children evaluated two years later when PbB levels were significantly reduced (Otto et al, 1982). Although the functional and clinical significance of these data is not clearly understood, the results suggest that SW voltage is sensitive to body lead burden in children.

With the exception of the paediatric lead data, the utility of ERSPs in neurotoxicological research has not been demonstrated convincingly. The problems which limit the clinical application

of the P300, noted above, pertain also to the CNV and other ERSP measures. Methodological difficulties further limit the application of ERSP measures in clinical and neurotoxicological research. Eye and body movements produce considerable artefact during recording. Trials in which eye or body movements occur must be rejected from signal averages. Eye fixation on a visual target is usually required to minimise eye movement artefact. The complexity and expense of computerised data acquisition and analysis systems also limit the application of ERSP methods.

In conclusion, clinically validated sensory evoked potentials appear to be excellent candidates for human neurotoxicity testing. Event-related slow potentials, however, require standardisation, validation, and technological simplification before these measures are likely to provide any effective relief of our addiction to more traditional behavioural testing methods.

Discussion

Goffe: I am sorry to ask a simple question, but presumably these measurements are made as for measuring the EEG?

Otto: Yes, Electrodes are put on the scalp in the standard 10 or 20 positions.

Waldron: How practical would these tests be for use in the field? This might be one reason for not following them up. It is one thing to use tests in an exposure chamber study but it might be very different if you wanted to go into a solvent factory and look at an exposed population at work.

Otto: We are developing appropriate methodology for field testing, designed around a small microprocessor. I would limit field applications to the three clinically validated measures, since we know with a fair degree of certainty, what these measures mean, they are interpretable, and if there are increased latencies, these can be related to underlying morphological changes. The latency of the auditory brain stem potential varies

with temperature, so this has to be taken into account; this is true for somatosensory evoked potentials as well. For example, several years ago there was a report on the effects of alcohol on the auditory brain stem potential that has subsequently been shown to be an artefact, since when one drinks heavily, the core body temperature is reduced, and the change that was seen was probably due to a drop in body temperature.

Jamie: Does not the robustness of the tests suggest that their practical application is going to be limited?

Otto: I have some results with auditory brain stem potentials in rats exposed to n-hexane. The animals were exposed to 500 ppm, 1000 ppm and 1500 ppm of n-hexane continuously for 11 weeks and then there was a 13 week recovery period when exposure was withdrawn. During the period of exposure, there was a good dose-response relationship but what is of interest is that after the recovery period there was little apparent recovery, at least at the highest level. At the lower level there was some recovery of function.

Wilkinson: I think the short latency potentials you mentioned initially might be very useful if they are not affected by attention. The test involving longer latencies, the one using the reversible checker board technique is, I think, going to be affected by attentional factors.

Since the toxic substances we are concerned with do affect attention, would it not be easier simply to study them by behavioural tests rather than by more complex techniques of evoked potentials which to a certain extent do relate to behaviour although the basis of these relationships is not clear. So where attention comes in why not use behaviour and where it does not use the short latency brain stem potentials?

Otto: There is evidence that the visual evoked response is not greatly affected by attentional changes. The subject has to fixate on the stimulus, obviously. Beyond that, there seems to be little effect. I think that we can gain additional information by using behavioural and electrophysiological measures together, since the two are obviously directly related.

5. SOLVENT METABOLISM: INTERACTIONS AND IDIOSYCRASIES

H.A. Waldron and Nicola Cherry

There are three interactions which are of importance when considering the neuropsychological effects of solvents, solvent-drug, solvent-solvent, and solvent-alcohol interactions.

Solvent-drug interactions

The effect which solvents have on drug metabolism is, in general, related to their hepatotoxicity. Compounds such as chloroform and carbon tetrachloride which cause hepatocyte damage reduce the rate of drug metabolism by interfering with normal hepatocellular function. By contrast, solvents which are less toxic to the liver, such as methyl chloroform, styrene, xylene and MEK, may increase the rate of drug metabolism by hepatic enzyme induction (Fuller et al, 1970; Vainio and Zitting, 1978; Toftgård et al, 1981). Drugs which themselves induce the P450 linked mixed function oxidases will speed up the rate at which those solvents depending upon these enzymes for their metabolism are degraded.

The role of biotransformation is highly important when considering the toxicity of organic compounds. Drugs which enhance the metabolism of solvents will decrease their toxicity if the parent molecule is the actual toxic agent. When metabolites are the toxic agents, then the toxicity of the parent compound will appear to be enhanced by drugs which speed up the rate of biotransformation. For example, the hepatotoxicity of carbon tetrachloride is enhanced by pre-exposure to enzyme inducers (Curtis et al, 1979) and it has been suggested that these compounds may increase the toxicity of styrene by stimulating the rate of production of styrene oxide (Parkki et al, 1976). It is possible that the toxic effects of n-hexane will be potentiated by inducers such as phenobarbitone since this stimulates hydroxylation in position 2, leading to an increase in the formation of 2-hexanol, the precursor of 2,5-hexanedione (Frommer and Ullrich, 1974).

Effects on Psychoneurological function

It is important to establish whether or not exposure to solvents has added effects in people who regularly take drugs. The size of the problem may be judged from the results of a cross-sectional study in which it was found that approximately 5% of males in the U.K. regularly take psychotropic drugs (Balter et al 1974).

Given the narcotic effects of solvents, it may be that interactions with psychotropic drugs are most relevant, but few studies have been undertaken in which the effects of psychotropic drugs on the performance of subjects exposed to solvents under experimental conditions have been examined. Ferguson and Vernon (1970) studied the effects of thonzylamine and meprobamate in combination with trichloroethylene and Stewart and his colleagues (1977) examined the interactions between diazepam and perchloroethylene. In no case was there any evidence for additive or synergistic effects. There is clearly further scope for studies of this kind, however.

Solvent-solvent interactions

The metabolism of benzene and its analogues is similar in many respects so it is not surprising that the co-administration of aromatic compounds results in the suppression of the metabolism of the compound which is present in the lower concentration. Thus, it has been found that toluene in excess will suppress the metabolism of xylene and styrene; the suppression is overcome by pre-treatment with phenobarbitone (Ikeda et al, 1972). At levels close to the threshold limit values, Sata and Nakajima (1979) were unable to show any metabolic interaction between benzene (25 ppm) and toluene (100 ppm) in human subjects, however, although interactions were readily demonstrated in animals given these solvents by intraperitoneal injection.

Interactions also occur between aliphatic solvents such as MBK and MEK (Abdel-Rahman et al, 1976) and there is also evidence that toluene and trichloroethylene impair each other's bio-degradation. In the latter case it has been shown that trichloroethylene is a non-competitive inhibitor of side chain hydroxylation of p-toluene

(a substrate analogue of toluene) but that toluene inhibits trichloroethylene metabolism in a non-competitive fashion (Ikeda, 1974).

Effects on neurotoxicity and performance

Under experimental conditions, it can be shown that the administration of MBK to animals may potentiate the neurotoxic effect of MEK (Abdel-Rahman et al, 1976; Saida et al, 1976) but, by contrast, toluene appears able to protect against the neurotoxic effects of n-hexane (Takeuchi et al, 1981). Interactions of this kind may be of importance in human toxicology and there is some evidence that exposure to solvent mixtures may potentiate the activity of weakly neurotoxic substances in the mixture (see the papers by Cavanagh and Venables in this volume).

Hänninen and her colleagues (1976) have suggested that exposure to mixtures of solvents may interact to cause behavioural effects at levels that would not be found for a single solvent. A group of car painters was found to perform significantly less well in a battery of psychological tests than a group of railway workers. The car workers were exposed to a mixture of solvents including toluene, xylene, butyl acetate, white spirit, MiBK, isopropanol, ethyl acetate, acetone and ethanol. Of these, however, only toluene was present in concentration in excess of 10% of the threshold limit value; toluene was present in a mean concentration of 30.6 ppm or 15.3% of the TLV. We have found only relatively minor effects in men who have been exposed to toluene in amounts much greater than this (see Cherry et al in this volume) and this is a matter which requires much greater study.

Solvent-alcohol interactions

Alcohol adversely affects the metabolism of xylene (Savolainen et al, 1978; Elovaara et al, 1980), toluene (Sato et al, 1980) and trichloroethylene (Muller et al, 1975). In our own studies we have shown that the co-administration of ethanol (1.5ml vodka/Kg body weight) causes a 42% increase in blood toluene concentration in volunteers exposed to 80ppm toluene in an exposure chamber (Waldron et al, 1983). We have also shown that alcohol impairs

styrene metabolism by inhibiting the breakdown of phenylethane 1,2 diol (Wilson et al, 1983). The effect of the interference with styrene metabolism is to delay the appearance of mandelic acid in the urine; a similar delay in the appearance of methylhippuric acid in the urine of volunteers exposed to xylene has been noted by Riihimaki and his colleagues (1982).

The delayed effects on the urinary excretion of metabolites follows the injestion of a large molar excess of ethanol. In rats given alcohol chronically it was found that the metabolism of some solvents (including toluene) was actually enhanced by the induction of hepatic enzymes (Sato et al, 1980). In men exposed to toluene at work we have found that blood toluene concentrations are lower in regular drinkers than in non-drinkers even though the levels of exposure were similar (Waldron et al, 1983). The effects of alcohol on solvent metabolism may thus be more complex than exposure chamber studies lead us to believe and are certainly worthy of further study among men who are exposed at work.

Behavioural effects

Experimental studies with human subjects suggest that alcohol augments the effects of trichloroethylene (Ferguson and Vernon, 1970) but not perchloroethylene (given at 100ppm) (Stewart et al, 1977). In our study of the interactions of toluene and alcohol (Cherry et al, 1983b) we found no overall interactive effects but there was a significant inter-subject variation, suggesting that there is a considerable individual variation in the response to solvent/alcohol mixtures.

Idiosyncratic effects

In our studies of styrene workers we showed that the metabolism of styrene varied between individual workers and that those who were excreting mandelic acid in an early morning urine specimen after a two or three day break, had slower reaction times than those whose urine was clear (Cherry et al, 1981). By analogy with what is known of idiosyncrasies in drug metabolism, it was not surprising to find a variation in the rate of styrene metabolism

but ours was the first demonstration of a behavioural effect related to apparent differences in metabolism. We have also found that a small proportion of men exposed to toluene (7-10%) return to work after a break with an unusually high exretion of hippuric acid. More interestingly, we find that the number of reported accidents over a three year period is related to early morning urinary hippuric acid concentration, an effect which appears to be independent of exposure (see Tables 5-1 and 5.2). These are preliminary results, but suggest an important area for further work.

Discussion

MacKay: How do the differences in the exoretion of mandelic acid relate to alcohol intake in the groups you have looked at?

Waldron: There is no difference in the reported alcohol intake between those who were exreting large amounts of mandelic acid in the morning and those who excreted none. Alcohol intake was the first explanation we thought of but it does not seem to be the correct one. Of course, we had no measurements of blood alcohol but we have good evidence that reported alcohol intake is a good measure of real intake.

Hernberg: I strongly believe that individuals vary in their sensitivity to solvents but I think there may be two factors involved. First, there is the rate of metabolism which may vary. Secondly, one has to consider which metabolite is the actual toxic agent. It may be a good thing to metabolise some solvents rapidly, or a bad thing, it depends on whether toxic metabolites are formed or not. These differences in metabolism, of course, mean that some individuals are effectively more heavily exposed than others, even if their intake is the s

TABLE 5-1

Morning hippuric acid (mmol/mmol creatinine) on first day after break

Job	Low accidents (0-10)	High accidents (11 and above)
Calender men	0.37 (n=15)	0.59 (n=4)
Body weighers	0.44 (n=3)	-
Surface weighers	-	0.54 (n=1)
Mixers	0.30 (n=3)	0.32 (n=2)
Others	0.39 (n=12)	0.54 (n=8)
Total	0.38 (n=33)	0.54 (n=14)

TABLE 5-2

Morning hippuric acid (mmol/mmol creatinine) on second day after break

Job	Low accidents (0-10)	High accidents (11 and above)
Calender men	0.59 (n=14)	1.35 (n=4)
Body weighers	0.41 (n=2)	-
Surface weighers	-	0.33 (n=1)
Mixers	0.42 (n=3)	1.41 (n=1)
Others	0.30 (n=12)	0.71 (n=6)
Total	0.45 (n=31)	0.95 (n=12)

$P<0.05$

Waldron: Your remark on toxic metabolites is most important. One thing we can say in connection with the mandelic acid and reaction time is that the mandelic acid is almost certainly not causing the effect; it is a marker for some metabolic difference, but at the moment we have no idea which metabolite in the pathway is causing the efect.

Gompertz: In our exposure chamber experiment, when we were exposed to styrene on two occasions, we found that there was a 56% decrease in blood mandelic acid concentrations when ethanol was taken (Wilson et al, 1983). This was accompanied by an increase in the concentration of the precursor of mandelic acid, phenylethan 1,2 diol; there was a 50% drop in the mandelic acid concentration but a fifteen fold increase in the concentration of the diol. This implies that the block is between the diol and mandelic acid. That is an oxidative step which uses NAD as a co-factor and I think that many interactions involving solvents and other substances such as ethanol are in fact a result of competition for co-factors such as NAD or NADP, and not necessarily competitive inhibition of enzyme activity.

Wilkinson: In a study (Wilkinson and Colquhoun, 1968) we did some time ago, on the interaction of alcohol and sleep deprivation we found that in some people the adverse effect of sleep deprivation on reaction time was reduced by alcohol and in some people it was increased. Those in whom it was reduced, were people with low blood alcohol levels.

Gamberale: The effects of alcohol can vary depending on whether you measure when the blood alcohol is going up or when the blood alcohol is going down. When did you measure blood alcohol levels?

Waldron: We put the people in the chamber for three hours then gave them the alcohol. After fifteen minutes they underwent forty-five minutes of testing, and we measured blood alcohol at the end of the experiment; it was an hour after they had taken the alcohol. In our more recent studies we insert a venous cannula so we can take blood in the exposure chamber every five or ten minutes. It will be interesting to see if the effect is related to the speed of metabolising the alcohol. The effects may also depend on how much the subjects normally drink; if they are heavy drinkers they will presumably metablise at a faster rate than if they are not.

Gompertz: In that experiment our alcohol intake in molar terms was 300 times greater than our styrene intake. With that amount of alcohol, hepatic metabolism was presumably completely swamped and the styrene metabolism stopped until the blood alcohol dropped down to a low level.

Axelson: Did you look for an effect of body mass effect on rate of excretion in your styrene worker?

Waldron: The slow excreters were not fatter than those who were getting rid of the solvent quickly. In fact, there were not any obvious differences between the two groups. We compared their size and shape, and their drinking habits and they seeemed identical.

Axelson: Would it be feasible to look at the effect of alcohol on the concentration of styrene or toluene in the brain in animals studies? You showed an increase in blood concentrations, but what do you think happened to the concentration in the brain?

Waldron: This would be a most interesting thing to do experimentally. On this question of solvent alcohol interactions, it is important to separate behavioural changes due to alcohol from those due to styrene. Lindstrom and his colleagues (1978) looked at some styrene workers and suggested that it was possible to

separate the effects which were due to styrene from those which were due to alcohol, and, bearing in mind that alcohol exposure is likely to be much greater than the solvent exposure, it is oearly important to be sure that you are dealing with solvent induced effects rather than alcohol induced effects.

Gompertz; I think we might mention our negative study on 1-1-1-trichloroethane here. Andersen (1981) considers that solvent metabolism is perfusion-limited rather than metabolism-limited and we wondered whether the effects of some of these alcohol solvent interactions were due to the solvent altering the perfusion of the metabolising organ rather than altering the metabolism itself. We used 1-1-1-trichloroethane as a non-metabolised solvent and repeated the styrene experiment, and there was no effect whatsoever on levels in either the blood or the breath. This demonstrates that you do need a metabolic interaction for changes to occur.

Gamberale: In an exposure chamber study we exposed 16 persons for four hours to toluene at the TLV, and on another occasion to xylene also at the TLV. On neither occasion were there any behavioural changes. They were also exposed to both solvents at the same time and we still found no effect. Nor was there evidence of any interaction. We also looked at the uptake of the solvents but again there was no evidence for any interactive effects.

6. DANISH EXPERIENCE WITH WHITE SPIRIT

K-H Cohr

For fifteen to twenty years, house painters in Denmark have complained of work-related symptoms referable to the mucosae and the nervous system, especially the central nervous system. In the early 1970s, two student reports appear which gave an account of these symptoms in house painters, based on interviews (Glud et al, 1971; Andersen et al, 1972).

The appearance of the complaints seemed to be related to the introduction of new types of paint. From the late 1950s onwards, oil paints containing 15-20% of white spirit have been substituted by alkyd paints containing about 40-50% of white spirit. Furthermore, new techniques such as spray painting and rolling were used and the new alkyd paints were used on large surfaces such as walls and ceilings. These changes all resulted in a great increase in exposure to white spirit.

Chronic effects

It was believed that the neurological symptoms attributed to house paint were acute effects which would disappear when exposure was discontinued. As time passed, more painters were shown to have the symptoms which appeared to become more severe and persistent. The complex of neuropsychiatric symptoms was later described as an organic cerebral syndrome said to resemble presenile dementia. The syndrome is now called chronic toxic encephalopathy.

In 1976, brain damage resulting from long-term occupational exposure to organic solvents was acknowledged by the Danish authorities; the first disability pension was awarded to a house painter exposed to white spirit. Before that date, a disability pension had been awarded only if brain damage was considered to be caused by accidental high exposure to organic solvents.

In a two-year follow up study at the University of Copenhagen, 26 house painters diagnosed as having presenile dementia were

re-examined (Arlien-Soborg et al, 1978, 1981; Bruhn et al, 1981). From the replies given to a questionnaire it seemed that some of the patients had shown an improvement in asthenic symptoms but the majority showed no improvement or reported that they were worse. There was no improvement in intellectual impairment or in many emotional symptoms, but other non-specific symptoms, such as headache and giddiness were improved (Table 6-1).

The patients completed a battery of neuropsychological tests and the results were compared with their previous scores. The grouped results are shown in Table 6-2. Twenty four of the twenty six patients showed no change in performance; the two other patients had deteriorated.

In 1979, the patients had had pneumoencephalograms and CAT-scans performed. Nine had no abnormalities, twelve had cortical atrophy and five had central cortical atrophy. In the follow-up two years later, the degree of cortical atrophy was more severe in two cases but in the remainder there was no change.

From these results it seems that exposure to white spirit may cause damage to the brain as revealed by changes in personality and by performance in neuropsychological tests. In some cases it is possible to demonstrate cerebral atrophy.

Other reports from Denmark describe the same picture for other groups occupationally exposed to different organic solvents and since 1976, about 700 workers have been awarded disability pensions. This indicates that we are dealing with a general solvent effect.

Acute effects

In 1975, at the Danish National Institute of Occupational Health, we initiated studies of the acute effects of white spirit. We have undertaken two series of experiments in a dynamic flow exposure chamber.

In the first series of experiments, three groups of male volunteers were exposed to white spirit, type V (see Table 6-3) under the following conditions (Stokholm et al, 1979a, 1979b; Cohr et al, 1980):

Symptom	1979	1981			
	Present	Disappeared	Better	Same	Worse
Asthenia					
Tiredness	26	3	6	14	3
Reduced initiative	11	1	1	9	0
Intellectual impairment					
Memory	25	0	4	19	2
Attention	20	1	1	17	1
Emotional symptoms					
Irritability	19	0	11	7	1
Nervousness	12	0	0	11	1
Depression	6	0	0	6	0
Emotional lability	14	0	1	12	1
Other symptoms					
Headache	19	3	12	3	1
Giddiness	23	5	12	5	1
Alcohol intolerance	9	1	1	7	0
Sweating	11	1	2	8	0
Sexual dysfunction	10	1	0	8	1

Data from Arlien-Soborg et al, 1981.

TABLE 6-1. Number of reports of neurological symptoms amongst 26 house painters in Denmark.

Group 1: Students at rest, 0, 34, 100, 200 and 400 ppm;
Group 2: House painters at rest, 0, 50 and 100 ppm; and
Group 3: Students at rest/intermittent work load (50W), 0, 50 and 100 ppm.

Exposure time was seven hours and the subjects acted as their own controls in a latin square study design. Amongst the effects looked for were mucosal and neurological symptoms (from questionnaires) whilst objective effects were recorded by means of a clinical neurological examination and neuropsychological testing.

With the exception of two of the neuropsychological tests, no effects were found in Group 3 and they will not be discussed further.

The mucosal symptoms most frequently reported by the house painters were irritation of the eyes, running nose and a strange taste in the mouth. The students, on the other hand, reported only eye irritation and running nose. In the students, but not in the house painters, there was an increase in neurological symptoms (headaches, giddiness and tiredness). In the clinical examination of the students, the Romberg test and walking with eyes closed were affected whereas in the house painters, only the Romberg test was affected.

The subjects completed a battery of four neuropsychological tests, simple continuous reaction time, a paced auditory serial addition test, the Purdue pegboard test and short term and long term memory tests. The students were significantly affected in the first three tests and the painters had prolonged reaction times. In the memory tests there was an interesting difference between the students and the painters. The former had a reduced performance in the long term memory test whereas, in the painters, short term memory was affected in addition to being unable to cope with the long term test of memory (Figure 6-1).

The effects on the students were noted at the higher levels of exposure (200 and 400 ppm) whereas the house painters were affected at lower concentrations (100 ppm). It remains to be seen whether this difference between the students (aged between 22-28 years)

	1979				
1981	0	0.5	1.0	1.5	2.0
0	2				
0.5		5			
1.0		1	8		
1.5			1	3	
2.0					6

Data from Arlien-Soborg et al, 1981.

TABLE 6-2. Degree of reduction in performance in neuropsychological tests amongst 26 house painters in Denmark.

and the house painters (aged between 31-69 years) is a result of age, of occupational exposure or of both.

In the second series of experiments, two groups of male volunteers were exposed to white spirit as follows:

Group 1: Students at rest, 0, 50, 100 and 200 ppm of type E only (see Table 6-3);

Group 2: Students at rest, 0, and 100 ppm of types V, E and S.

Exposure time was six and a half hours and the subjects acted as their own controls in a latin square study design.

In these experiments only long term memory was found to be affected and, as may be seen from Figure 6-2, type S had the largest effect of the three types of white spirit used.

Chemistry

White spirit is a generic name for solvents which may contain between 150-200 hydrocarbons and which are used mainly as paint solvents and dilutants. Three typical gross compositions are shown in Table 6-3. These three types have boiling points in the temperature range 160-190°C. There are also types with high boiling points but they have special applications. Type V is the kind of white spirit that was used in Denmark in the 1960s and 1970s. It contains 17-18% of aromatic hydrocarbons, 25% of naphthenes (cyclic aliphatic hydrocarbons) and about 55% of paraffins (saturated aliphatic hydrocarbons). From the mid 1970s, there has been a tendency to shift towards the use of the so-called odourless or de-aromatised white spirits which contain almost no aromatics. Two typical examples as types S and E shown in Table 6-3. The latter type is produced from type V by hydrogenation of the aromatics which are converted into naphthenes. Type S is de-aromatised in another way, resulting in a mixture of paraffins only. These differences in composition may give rise to differences in toxicokinetics.

		S	E	V
Paraffins	C_8	0.12%	0.9%	1.0%
	C_9	0.77%	10.4%	11.4%
	C_{10}	15.0%	22.4%	24.6%
	C_{11}	38.7%	14.5%	15.9%
	C_{12}	44.4%	3.7%	4.1%
	Total	98.9%	52.0%	57.0%
Naphthenes	C_8	-	6.1%	4.5%
	C_9	0.15%	14.2%	5.1%
	C_{10}	0.94%	19.1%	8.7%
	C_{11}	-	6.8%	5.4%
	C_{12}	-	1.7%	1.3%
	Total	1.1%	47.9%	25.0%
Olefines	Total	-	-	1.0%
Aromatics	C_8	-	-	1.5%
	C_9	-	-	8.1%
	C_{12}	-	-	8.2%
	Total	-	-	17.8%

TABLE 6-3. Hydrocarbon content of different types of white spirit.

Toxicokinetics

The three types of white spirit shown in Table 6-3 have different modes of uptake, distribution and accumulation. Sixty five percent of an inhaled dose of the type E and type V hydrocarbons is retained in the body, whereas for type S, the retention is about 35%. The retention rate of the aromatic hydrocarbons is about 85%. These figures are based on measurements carried out on volunteers at rest. When a person is exposed during a work load, the relative uptake decreases, but since the respiratory minute volume increases, the retention per minute also increases; in the case of a 50W work load, the retention of aliphatics is doubled.

The uptake of aliphatic hydrocarbons during exposure to type V white spirit is shown in Figure 6-3. The area below the curve (open triangles) is a measure of the amount taken up during exposure. The concentrations in the alveolar air falls rapidly after the end of exposure (filled triangles). During the first ten minutes after exposure, the concentrations in the alveolar air decreases to 10% of the concentration in the alveolar air during exercise.

It may be calculated that only 10% of the amount retained is exhaled during the first seventeen hours after the end of a seven hour exposure period. This indicates that the hydrocarbons are accumulated in tissues with a long biological half-life (estimated to be in order of 80 hours). This observation is supported by showing that the concentration of aliphatic hydrocarbons in venous blood during seven hours exposure to type V white spirit at rest continues slowly to increase. Thus, under these conditions, a steady state is not achieved.

Some of the retained hydrocarbons are biotransformed, primarily in the liver (Table 6-4). Hydrocarbons are oxidised by mon-oxygenases of the P-450 microsomal enzyme system. The oxidation site in the molecule depends on the chain length, saturation and reactivity of the carbon atoms; the oxidised products are excreted in the urine after coupling to hydrophilic molecules.

Enzymes	P-450 microsomal enzyme system
Oxidation products	
Saturated aliphatics	
Less than 10 C-atoms	2- and 3-alcohols
More than 10 C-atoms	1-alcohols, acids
Reactivity of C-atoms	$C_{tert} > C_{sec} > C_{prim}$
Unsaturated Aliphatics	
Double bonds	Epoxides, di-alcohols
Triple bonds	?
Aromatics	
Without side chain in the ring	Phenols via epoxides
With side chain in the ring	Alcohols, acids
Excretion products	
Coupled to	Glururonic acid
	Amino acids (e.g. glycine)
	Glutathione (mercapturic acids)
	Sulphate (ethers, esters)

TABLE 6-4. Biotransformation of hydrocarbons

Discussion

O'Hea: What have been the practical results of your studies in Denmark? Have the standards been changed? Is there better ventilation in the rooms that are being painted or is everything going on as before?

Cohr: Restrictions are going to be introduced, not on the total area which can be painted, but if the surface is more than a certain area, painters will be required to wear charcoal filter masks.

Ron: I am bit concerned about the use of the term presenile dementia; it is important that we know exactly the condition we are describing. I have the impression that the patients you were describing did not have the clinical picture that we would associate with Alzheimer's disease or that type of cortical dementia. I also have a strong impression that of the twenty-six patients you described only two seemed to have got worse when they were followed up. One of the cardinal points of a dementing illness is that it is a progressive condition but you seem to be describing a static state. Could you define more precisely what is meant by presenile dementia in your cases, and secondly, do you have any evidence that this is a dementing illness as opposed to damage which is static?

Cohr: I must say these were not my cases, I am merely giving the diagnosis made by the authors of the paper.

Axelson: I think this is an important issue. Epidemiological studies, of course, reflect the diagnoses that the neurologists put on their patients. If they call the condition presenile dementia, then it is presenile dementia in epidemiological terms and we cannot change that. In looking at the cases from the clinics it is difficult to differentiate between the true Alzheimer and other types especially since not all of them have been examined sufficiently to show if there really is cortical atrophy.

Gamberale: In Sweden we do not define the term dementia as you do in Denmark. Some Danish psychologists use the term dementia when they get results on psychological tests which they believe are not as they should be.

Cohr: That certainly applied to the psychologist at the university hospital in Copenhagen. But the term presenile dementia as used in the register investigation that I mentioned was taken from the journals of the workers, and this was the diagnosis made by the physician after he had examined the patients.

Ron: I am involved in a study of the psychological changes in chronic alcoholics and I would not want to call them demented on the basis of our findings. I would say that they suffered from some degree of neurological damage detectable by psychological tests, but we do not know the prognostic implications of these changes. We do not know how these psychological tests relate to any neuropathological change. But because the diagnosis of presenile dementia implies a condition which is progressive, I would not use it to decribe the people I have been investigating.

Lucas: From the practical point of view, would it not be reasonable to say that intellectual performance of those painters has deteriorated beyond what would normally be expected for their particular age range. That would get us off the hook of presenile dementia, would it not?

Wilkinson: Can I ask what the normal expectancy for that age is? Secondly, you had performance measured in 1979 and again in 1981 and you said there was no change. What was the control group for that assessment? You would expect the same people to change from the first to second occasion of testing.

Cohr: The subjects were compared with patients admitted to the university hospital for some reason other than neurologicl cause.

Wilkinson: Was the time interval between testing the same? This is a very important factor.

Cohr: I do not know that, I am afraid.

Hernberg: I think we must not get too involved with semantics. The most important thing is that we have two groups (painters and bricklayers) with the same system of diagnosis and there is a two fold difference between the groups. There may be some misclassification, of course, but there could be no systematic error which could account for the difference.

Carter: Have studies been performed on new entrants to house painting to evaluate their cognitive functions; is it a job for people with inherently poor mental abilities? You mentioned the two studies carried out in Copenhagen; is this a problem limited to Copenhagen, or are there similar reports from elsewhere in Denmark?

Cohr: There are often reports from Denmark. As to your other question, in Sweden and in Finland psychological tests are carried out on volunteers for the military, and those men who afterwards become painters are no different from others who go on to different jobs.

Axelson: In Sweden this will apply to all the military, not just volunteers.

Gamberale: We must be careful in our interpretation of those results. The tests carried out ten years ago were very different from those used in our studies now. The former tests were probably not sufficiently sensitive to enable us to conclude that the groups were similar with regard to performance.

7. DOES SOLVENT POISONING EXIST?

S. Hernberg

The question which is posed in the title of my paper can be answered very simply; it is yes, solvent poisoning does exist. Having given this answer I propose to review some of the studies from the Institute in Helsinki from which I think we have evidence supporting this statement.

First of all we have clinical experience. This is of course not scientific proof. However, since the 1960's we have had, in Finland, about 600 cases of solvent poisoning which have been compensated by the insurance companies. So there is a considerable number of patients who have given us clinical experience. In addition to these observations on patients we have done some clinical, and several epidemiological studies where we have been dealing not with single patients, but with groups. I will discuss both types of study but before I do so, I will discuss some definitions.

The old classification of occupational disease meant a frank clinical condition, but I am not going to stick to this definition because I feel it is outdated. I would like to stress the existence of subclinical and reversible stages; stress that there are several degrees of illness. Moreover, in my terminology I do not equate "chronic" with irreversibility. Instead, I take chronic to mean of long duration; the effects may be reversible or irreversible.

In epidemiological studies of large groups every subject cannot have a thorough clinical examination. Instead we look at statistically significant differences, as compared with a reference group, on one or more clinical, physiological or psychological measures. In these studies we are not so much concerned with individual clinical diagnosis, but with the diagnosis of harmful work conditions. We should also recognise that if a signficiant group effect is found, then it follows that there will be some

unspecified individuals who are below the "normal" level as a consequence of the distribution of effect, but they are unspecified because at that stage nobody has had a complete clinical examination. The next step is to identify and examine the abnormal individuals. I repeat, however, that the individual diagnosis of poisoning can never be based on group differences only. It must be based on clinical examination using criteria I shall refer to later.

Valid epidemiological studies with "positive" findings are the best evidence that solvents exert toxic effects. In clinical studies it is hard to avoid circular reasoning, and thus the results of epidemiological studies must be the primary aetiological evidence. Clinical studies can be used in support of the epidemiological results but not as a primary source of evidence.

First I shall briefly describe a study of car painters (Husman, 1980; Husman and Karli, 1980). Their overall exposure (sum of many solvent components) was about one third of the American TLV and from estimates given by some of the older employees, it is likely that only small changes in exposure had occurred over a 10 year period. The acute symptoms found in these car painters are shown in Table 7-1. There are many differences in the prevalence of these acute symptoms in the painters compared with a reference group. There was also a difference in more long term symptoms (Table 7-2), and, of course, there were several other symptoms which did not show any difference. The questionnaire used in the study contained about thirty different questions, some of which were dummy questions which could not relate to solvent exposure. Without exception, answers to these dummy questions were evenly distributed between the groups.

The painters also had some objective signs. Vibration sense was diminished in 43 of the 102 painters compared with 17 of the controls. There were also some minor changes in light touch and pain modalities in the left hand and left foot; the left was chosen for testing because right handed persons usually have thicker skin on the right hand. The changes that were found are of no great health significance but they show that there is a difference between the exposed and non-exposed groups.

TABLE 7-1

Significant differences in prevalence of acute symptoms (related to a specific workday) between 102 car painters and their pair-matched controls (Husman, 1980)

Symptoms	P-value <	$X^2(2)$ (Stuart)
Itching	0.05	6.60
Feeling unwell	0.001	13.82
Nausea	0.05	8.63
Dizziness	0.01	12.63
Feeling of drunkenness	0.001	37.1
Breathlessness	0.01	11.58
Absentmindedness	0.001	23.26
Misunderstanding of given instructions	0.001	16.76

Psychological testing also revealed group differences. Impairment in visual intelligence and verbal memory were the central features, but verbal intelligence was also affected (Hänninen et al, 1976). The tests were carried out on a sample of 100 pairs (exposed and non-exposed men). Among them there were 33 pairs for whom the results of tests which they had performed during their military service were available.

These earlier results showed that the painters did not differ then from their referents. This suggested that the differences found in the psychological tests between the car painters and the referents were not because of pre-existing differences but had probably resulted from solvent exposure.

We have also looked at a group of 12 men exposed to n-hexane at about the present hygienic level (Seppäläinen et al, 1980). The frequencies of complaints were so high that a reference group was unnecessary. Most of the EEG examinations were borderline or abnormal. What was interesting was that there was a connection between the number of symptoms reported and the frequency of abnormal EEGs; the more symptoms, the more abnormal was the EEG. Eleven of the men had some abnormal conduction velocities or an abnormal EMG and they also had colour vision changes, particularly affecting blue and yellow vision which is an acquired effect. In this small group, then, there was not one normal person.

The next study I shall review was carried out in workers exposed to styrene (Härkönen, 1977, Härkönen et al, 1978 and Seppäläinen and Härkönen, 1976). In this study there was an attempt to make some exposure-response evaluations. The urinary mandelic acid concentration was used as an indicator of exposure. There was a relatively wide scatter when comparing mandelic acid and atmospheric levels but this is not surprising in view of the differences in physical activity, for example. A mandelic acid concentration of 700 mg per litre corresponded on average to an eight hour exposure of 30 ppm. For the exposure-response evaluations, mandelic acid concentrations were determined five times during five weeks, the first week on Monday, the next week

TABLE 7-2

Significant differences in prevalence of more longstanding symptoms between 102 car painters and their pair-matched controls (Husman, 1980)

Symptoms	P-value <	$X^2(2)$ (Stuart)
Unusually tired after the workday	0.05	7.99
Unusually tired in the morning	0.05	7.30
Absentminded	0.001	16.76
Forget easily what you intend to say or do	0.001	21.51
Easily fall asleep when watching TV	0.05	6.58
Daydreaming	0.05	7.12

on Tuesday, the following week on Wednesday, then on Thursday and finally on Friday, that is to reflect not only the weekly average but also to reflect the daily average. Amongst those men who had a mean mandelic acid excretion of less than 700 mg/l, there were about 10% abnormal EEGs. This is the proportion normally found in referent subjects in our laboratory. With mandelic acid concentrations above 700 mg, the proportion of abnormal EEGs was between 30 and 40%. So this is some indication of an exposure-response effect. In this group of men there were no abnormalities nor any group differences in the peripheral nervous system. With some of the psychological tests, however, we also found a tendency towards an exposure-effect relationship between mean mandelic acid concentration and test performance. The threshold in this case seemed to be about 1600 mg/l suggesting that EEG changes precede the psychological effects. The health significance of these changes is again unclear, but taken together, there is indication of impaired CNS function which is evident in both the psychological tests and in the EEG. The exposed workers also complained of more subjective symptoms than the controls.

Several studies, not only from Finland but also from Sweden (Elofsson et al, 1980, Hane et al, 1977), have shown that workers who are exposed to various solvents and solvent mixtures have a pattern of symptoms and signs which may be related to exposure level. It may be that when exposure is discontinued, for whatever reason, the symptoms subside, but if workers are exposed every day, the symptoms persist for day after day, and what they experience is like a chronic hangover.

A summary of the EEG examinations on various exposed groups, conducted at the Institute is shown in Table 7-3. About 10% of non-specific changes are found in normal subjects and this is the proportion found in house painters who were exposed to rather low levels of solvent. On the other hand, 31% of car painters had EEG changes, and even higher proportions occurred in patients diagnosed as having solvent poisoning. The type of abnormalities included diffuse slow wave changes, focal changes (in 19%) and

paroxysmal changes (in about 5%). Of course, one may ask if all these changes are really due to solvent exposure, because of the "background noise" of about 10%, but it has not been possible to differentiate the aetiology of individual cases.

At the group level there seems to be little doubt that effects really can be shown, but what about a syndrome that we could call clinical poisoning? I believe such a syndrome exists, but one has to be aware of the danger of circular reasoning when defining it. Patients usually come to the Institute because solvent poisoning is suspected. If there is a history of exposure, a "typical" clincal picture, and if we can exclude other aetiologies, then the patients are given a diagnosis of solvent poisoning. Of course, this group of patients must exhibit a high frequency of abnormalities, such as EEG changes or whatever else has been used as a criterion of diagnosis. But as these findings were pre-requisites for the diagnosis, it would be circular reasoning to say, on the basis of clinical observations only, in cases of poisoning there is a high prevalence of EEG and other findings. This is the main reason why I prefer to base my case on epidemiological rather than clinical evidence even though we are then often dealing with isolated symptoms and signs, and often with rather early manifestations.

For descriptive purposes, however, we may learn something from studying clinical patients. At the Institute, where all patients with suspected solvent poisoning are sent from the whole country, we have developed standardised criteria for diagnosing solvent poisoning. The criteria are as follows (Juntunen et al, 1980). First, the quantity and quality of exposure to organic solvents (or any other neurotoxic substances) must be verified. Secondly, the patient must exhibit a "typical" clinical picture. This syndrome comprises subjective symptoms together with clinical neurological signs or psychological changes or changes in the EEG or ENMG. Thirdly, to exclude other organic diseases, the patient is seen not only by a specialist in occupational medicine but also by a neurologist and usually by a psychiatrist. The patient may

also be seen by a general physician, an otologist and an opthalmologist if there are special reasons, and we usually carry out neuroradiological examinations. If there is need for more specific tests, such as a CAT scan, we consult the University Hospital of Helsinki. From these examinations we can be reasonably certain to diagnose or exclude other conditions. If we really find no other explanation, if there indeed has been exposure and if there are "typical" symptoms and signs, then we feel the most likely diagnosis is solvent poisoning. The diagnosis can sometimes be straightforward, but in many instances it is very difficult and the formal decision to label the disease as occupational in origin may take several months of follow-up.

The clinical picture of solvent poisoning can then be described as follows: The subjective symptoms are similar to those reported in epidemiological studies, that is headache, fatigue, memory disturbances, nausea, dizziness, tremor, and subjective psychic and sensory disturbances. The subjective symptoms are accompanied in many instances by objective neurological changes, most of them slight, and most affecting the cranial nerves although in some cases there are extrapyramidal and cerebellar signs; sensory disorders are common. Objective psycho-organic changes are often present. EEG disturbances are common and slight pathological changes of the peripheral nerves are also often recorded. In a study on 37 patients, who had been thoroughly examined according to the scheme above, we noted many such findings. For example, pneumoencephalograms showed that cerebral or cerebellar atrophy was relatively common, although usually slight (Juntunen et al, 1980). In all, 24 patients had some changes. Table 7-4 shows the details of this examination. For the same patients, the EEG examination showed a high frequency of abnormalities (23/37), mostly with diffuse slow waves, but three patients also had spike and wave discharges. Changes in peripheral nervous system functions were noted in 23 patients of those 28 who underwent these tests. Psychological disturbances occurred in almost all

TABLE 7-3

Frequency of abnormal EEGs among solvent exposed workers (Seppalainen, personal communication)

	N	%
Repair painters in building industry	72	17
Car painters	102	31
Solvent exposed workers with symptoms	240	40 - 72
Patients with solvent poisoning	107	65
Patients with solvent poisoning	87	67

TABLE 7-4

Pneumoenephalographic (PEG) findings in 37 patients with solvent poisoning (Juntunen et al, 1980)

	Number of Patients			
	Slight	Moderate	Severe	Total
Cerebellar atrophy	5	0	0	5
Cerebral central atrophy	12	4	1	17
symmetric	5	1	0	6
asymmetric	7	3	1	11
Cerebral cortical atrophy	12	5	1	18
diffuse	5	0	0	5
localized	7	5	1	13

patients in different combinations; most patients had personality changes and problems of memory, learning and intelligence. The results of this study support the view that there really exists a clinical picture which can be classified as solvent poisoning.

When regarding symptoms and signs induced by solvent exposure, we have to distinguish between acute and chronic effects. As for acute effects, which are related to the presence of a solvent in the nervous tissue, we do not know if different types of solvents cause different symptoms or if the symptoms are due to a general narcotic effect and are related to the fat solubility of the solvent, for example. Nor do we usually have any clear evidence for deciding whether it is the solvent as such or its metabolites which cause the effects. The acute effects are, of course, easily reversible. With regard to chronic effects, they represent metabolic or anatomical damage to the nervous system, such as for example brain atrophy or axonal degeneration of peripheral nerves. Such effects are not easily reversible, even though regeneration or repair of function by means of compensatory mechanisms may occur.

Finally, I think it would be interesting to speculate why the majority of solvent workers do not exhibit any major symptoms of toxicity. The explanation could be due to the fact that sensitivity to solvents has a normal or skewed distribution, and only those who are at the most sensitive end of the distribution get ill. This could explain why it is not easy to get a clear exposure-response relationship, since the sensitivity of the patient then may be more important in determining the outcome than the exposure level. There may also, of course, be interactions with alcohol consumption, with infections, and with other, as yet unknown factors. Nevertheless, in spite of the many questions still unanswered, I believe that there is an entity which we can name solvent poisoning, which first effects the most sensitive individuals in an exposed population.

Discussion

Cavanagh: Were any nerve biopsies done on any cases that had abnormalities in the peripheral nerve so as to find out what in fact was the possible basis of this? The lesions of carbon disulphide are specific and I find it hard to believe in a sort of "generalised solvent" effect.

Hernberg: We have considered doing nerve biopsies but came down against it because it would produce a small anaesthetic area. We decided that we could not justify this on ethical grounds because the clinical diagnosis would not change very much on the basis of biopsy findings.

Cherry: I would like to concentrate on the epidemiological surveys rather than the clinical evidence since, as you say, it is so full of methodological problems. Of the three other studies you presented, one was n-hexane which I think we all accept, one was styrene which I think most of us might now accept given the high level of mandelic acid and third was the car painters where the exposure was a third of the TLV. It is that study which causes me the most problems because I do not believe that that degree of exposure could give those effects; 40% of vibration loss, for example, seems very high. In the study where we have been looking at people exposed to toluene with much higher levels there is virtually no effect. Perhaps we should all keep in the back of our minds the possibility of other causes for the effects which are found.

Hernberg: It is possible that our estimate of exposure level was too low.

Cherry: That is possible, but in one study you did actually mock up the best possible workplaces of 20 years ago and did not find levels as high as TLV. Is your feeling really that these are genuine solvent effects?

Hernberg: TLVs are administrative, not medical, standards and they may be too high, as often experienced before.

I agree with you that we must always try to look for other causes, but these were the findings of a trained neurologist and I am inclined to believe them.

Lucas: In doing this work has previous personality and psychiatric morbidity been looked at?

Hernberg: Yes, not only that, there was also an enquiry amongst car painters who had left employment, asking how they felt and why they left and so on. There was a higher than expected percentage of workers who said that they left for health reasons or that they did not feel very well, and most of them said they felt better when they had left the job.

Axelson: I would like to question the validity of the EEG findings because I think there is some discrepancy between practice and viewpoints in Sweden and Finland. At a recent meeting in Sweden of neurophysiologists, psychiatrists, neurologists and occupational physicians the conclusion was that one should not put too much reliance on abnormal EEGs and it was even suggested by some people, for example, that an abnormal EEG was evidence against solvent injury disorder; that was a statement which surprised me but it was said there.

Hernberg: All the examinations were done by Dr. Seppäläinen at our Institute. I think I would want her or another neurophysiologist to answer, I do not feel competent to common on those points.

8. LONG TERM NEUROPSYCHOLOGICAL EFFECTS OF SOLVENT ABUSE

Mary King

The present increase in solvent abuse, mainly as glue sniffing in underprivileged adolescents, represents a unique, unfortunately living, model of high exposure toxicity. Although recreational inhalation of gaseous and volatile substances seems a modern phenomenon, reports of such behaviour date back to the beginnings of Western civilisation. The Greeks are reported to have inhaled "trance inducing fumes" (Brecker, 1972) and the 18th Chapter of Deuteronomy refers to people inhaling vapours to alter their mental state. The era of recreational use of gaseous substances dates from the late 18th century with the discovery of nitrous oxide and ether.

Reports of solvent inhalation for narcotic effects appeared sporadically over the last 100 years until Clinger and Johnson (1951) reported an outbreak of gasoline sniffing among adolescents in Pennsylvania. Over the following two decades numerous further reports appeared in the American literature (Glaser and Massengale, 1962; Barker and Adams, 1963; Dodds and Santostefano, 1964; Knox and Nelson, 1966; Press and Done, 1967). Only three (single) case reports appeared in the United Kingdom over the same period (Merry and Zachariadis, 1962; Merry, 1967; O'Brien, Yosman and Hobby, 1971). However, in 1977, Oliver and Watson reviewed fifty cases of solvent abuse in Scotland. It is now apparent that solvent abuse is an increasing problem among adolescents in this country; in Scotland alone, in 1980, 1300 new cases were reported to the police from a secondary school population of almost half a million. Significantly, there have been at least sixty deaths following solvent abuse in the U.K. in the period 1970-81. Cohen (1978) estimated that 100 young persons a year die in the United States from the injudicious intake of commercial solvents (excluding deaths from asphyxia or accidental injury while intoxicated). The same study attempted to determine reasons

for solvent abuse and found the following: peer group influence, low cost, unrestricted availability, convenient packaging, rapid intense intoxication and absence of legal issue.

Morbidity studies on solvent abusers are difficult to interpret; in our experience a deprived social background is usual, as is under-achievement at school. Denial of solvent abuse is to be expected as is unreliability in identifying the preparations used, the duration and intensity of exposure or concomitant abuse of other drugs, notably alcohol. Finally, follow-up is obviously diffcult in this group, leaving major queries unresolved, such as the possible reversibility of toxic effects on withdrawal from solvents.

Studies on solvent toxicity in animals and in humans following industrial exposure form the basis for the TLV which refers to the airborne concentration of solvent to which it is believed workers may be exposed repeatedly without adverse effect (Utidjian and Weaver, 1974). The TLV for toluene is 100 ppm. Solvent abuse provides a uniquely high level of toxic exposure; the TLV may be exceeded several hundredfold so it is scarcely surprising that a significant incidence of solvent induced morbidity is seen in individuals who sniff solvents. This paper reviews the literature on long term neuropsychological effects of solvent abuse.

Reports from the literature and personal experience indicate that toluene is by far the most widely abused solvent. Toxic effects have been described on the gastrointestinal tract (Streicher et al, 1981), liver (O'Brien, Yeoman and Hobby, 1971), kidney (O'Brien, Yeoman and Hobby, 1971; Taher et al, 1974; Fischman and Oster, 1979; Moss et al, 1980; Kroeger et al, 1980; Streicher et al, 1981; Russ et al, 1981; Will and McLaren, 1981), muscle (Streicher et al, 1981), heart (Bass, 1970; Taylor and Harris, 1970), and central nervous system (Knox and Nelson, 1966; Kelly, 1975; Boor and Hurtig, 1977; Keane, 1978; Escobar and Aruffo, 1980; Malm and Lying-Tunell, 1980; Streicher et al, 1981; Fornazzari et al, 1982). The effects on the gastrointestinal tract, liver, muscle and heart appear reversible and resolve

following withdrawal from toluene. Renal impairment (acute renal failure, renal tubular acidosis, recurrent urinary calculi) appears reversible although one case of permanent renal failure has been recently reported (Russ et al, 1981). Bone marrow suppression, described in earlier reports (Greenburg et al, 1942; Wilson, 1943) followed use of preparations that contained up to 20% benzene and has not been reported with currently available preparations which contain less than 0.1% benzene (Fribroska, 1973).

In common with many other solvents the main toxic impact of toluene is on the CNS. The acute impact of solvents may be explained by a direct toxic action on the nerve cell membrane and intra-cellular metabolism, whereas chronic neurotoxic effects may be caused by the formation of chemically reactive intermediates differing with individual solvents. The possible chemical mechanisms of solvent neurotoxicity have been reviewed in detail by Savolainen (1977).

Acute CNS effects include euphoria, disorientation, lability of mood, tinnitus, diplopia, hallucinations, dysarthria, ataxia and coma. The immediate risks to the abusers include death from suffocation, accidental injury or cardiac arrhythmias (Winek and Collum, 1971). There is no correlation between acute clinical manifestations and subsequent long term sequelae inducible by chronic exposure to high or low concentrations of toluene.

There are no large studies on long term neurological sequelae of toluene abuse; information is limited to case reports which are summarised in Table 8-1. The table includes one case from a personal study detailed elsewhere (King et al, 1981). The commonest clinical presentation was one of a diffuse cerebellar encephalopathy with or without intellectual deterioration and dementia. Less frequent findings were optic neuropathy (Keane, 1978; Malm and Lying-Tunell, 1980; Fornazzari et al, 1982) and peripheral neuropathy (Streicher et al, 1981; Fornazzari et al, 1982).

LONGTERM NEUROLOGICAL EFFECTS OF TOLUENE ABUSE -
REVIEW OF THE LITERATURE

Author	Number of Patients	Age (Years)	Duration Exposure	Clinical Findings	Investigations	Outcome
Satran, 1963	1	30	11 yrs	Slow speech and Movement. Personality change	EEG ABM	Unknown
Knox & Nelson, 1966	1	33	14 yrs	Cerebellar, Corticospinal & Corticobulbar signs	EEG ABM PEG ABN	Unknown
Kelly, 1975	1	19	18 mths	Cerebellar signs	EEG N PEG N	Improved 5 months Later still ataxic
Boor & Hurtig, 1977	1	25	10 yrs	Cerebellar signs. Intellect dull	EEG N CT Scan ABN	9 months later unchanged
Keane, 1978	1	20	3 yrs	Cerebellar signs. Optic neuropathy demented	CT Scan N VER ABN	2 months later improved
Sasa et al 1978	1	27	12 yrs	Cerebellar signs. Equilibrium disorder	EEG ABN PEG ABN WAIS dull average	Unknown
Bennett & Forman, 1980	1	22	8 yrs	Cerebellar signs. Distal weakness.	CT Scan ABN Hypokalemia	Unknown
Malm & Lying-Tunnell, 1980	1	18	6 yrs	Cerebellar signs. Optic neuritis	EEG N CT Scan N	Asymptomatic 8 months later
Escobar & Aruffo, 1980	1	27	12 yrs	Confused Cerebellar signs. Weakness, sensory loss	EEG ABN CT Scan ABN NCV ABN	Died in hospital PM-diffuse cerebral atrophy with giant axonal degeneration
Streicher et al, 1981	10/25	18-40	Not known	Peripheral neuropathy 2 Cerebellar signs 3	Not recorded	Unknown
King et al	1/19	11-14	1 yr	Cerebellar signs	EEG ABN	18 months later persistent signs
Fornazzari et al, 1982	18/24	19-27	3-10 yrs	Cerebellar signs 11 Memory loss 5 Opticatrophy 1 Peripheral Neurop 1	CT Scan ABN	2/52 later No change

FOOTNOTE

E.E.G. : electroencephalogram
P.E.G. : pneumoencephalogram
C.T.Scan : computerised axial tomography scan
V.E.R. : visual evoked response
N.C.V. : nerve conduction velocity
W.A.I.S. : Weschler adult intelligence scale
N : normal
Abn : abnormal

TABLE 8-1

Electroencephalographic (EEG) and radiological findings were nonspecific; abnormalities (5/9) consisted of diffuse medium voltage slow wave activity and findings on pneumoencephalogram (2/3) and computerised brain scan (27/30) suggested cerebral atrophy with widening of cortical sulci and dilation of ventricles. Autopsy reports are few; Escobar and Aruffo (1980) reported cerebral and cerebellar atrophy and giant axon neuropathy affecting the long ascending and descending tracts. However, follow up in most of these cases is not adequate enough to permit an assumption of permanent neurological deficit. Prolonged follow up is clearly essential as severe neuropathy associated with other solvents, notably n-hexane, has been found to resolve completely several months following withdrawl (Paulson and Waylonis, 1976).

Long term psychological effects of toluene abuse are likewise poorly documented. Glaser and Massengale (1962) detailed six adolescents who presented with behaviour problems following glue sniffing but did not report formal psychological tests. Barker and Adams (1963) reported poor school adjustment and scholastic performance in chronic glue sniffers. Dodds and Santostefano (1964) compared twelve boys, mean age 13.8 years, who had been sniffing glue for three to forty-two months, with twenty-one age and social class matched controls and found no difference between the two groups on psychological testing. Press and Done (1967) in a review of solvent abuse included a personal study of sixteen patients, mean age 14.8 years, who sniffed glue for three months to three years prior to assessment and found poor scholastic performance in all areas tested.

In an attempt to evaluate these clinical findings in solvent abusers I have reviewed the literature on experimental studies in animals under conditions mimicking toluene abuse. Jenkins (1970) exposed rats, guinea pigs, dogs and monkeys to 1085 ppm toluene for eight hours daily, five days a week for eight weeks, or to 107 ppm toluene continuously for 90-127 days, and found no abnormal haematological or biochemical changes, or histological effects on heart, lung, liver, kidney in any species. Examination of the

brain and spinal cord in dogs and monkeys showed no abnormality. However, 2/15 rats died during continuous exposure at 107 ppm. Bruckner and Peterson (1876) exposed mice to 4000 ppm toluene for three hours on five days for each of eight weeks; although sufficient to produce acute intoxication, there was no detectable biochemical or histological effect on lung, liver or kidney. Takeuchi (1977) studied the effect of concentrations of 1000, 2000 and 4000 ppm toluene for four hours, on rat EEG and demonstrated a dose-dependent disturbance in behaviour and sleep cycles.

Ikeda and Miyake (1978) found reduced learning capacity in rats exposed to 4000 ppm two hours daily for sixty days. Contreras et al (1979) exposed cats to concentrations of 12000-52000 ppm for seven to forty days and studied the effects on behaviour and EEG. After a control recording, intoxication was commenced with concentrations of 12000 ppm gradually increasing to 20000 ppm with ventilation intervals of ten minutes, when electrical (diffuse slowing and 3HZ spike wave) and behaviour (head nodding, eye blinking, abnormal behaviour, facial twitching, ataxia) changes occurred. The animals recovered within twelve minutes of discontinuing inhalation. Although the amount of solvent to which the animals were exposed was high, duration of exposure was only a few minutes, whereas in man, self administered exposure is often of several hours duration.

Bruckner and Peterson (1981) exposed rats and mice to 4000-12000 ppm toluene (seven cycles daily of ten minutes inhalation followed by twenty minutes recovery, on five days for each of eight weeks) and acetone (19000 ppm three hours daily for eight weeks). They found that although toluene was a potent and rapidly acting narcotic, the animals quickly recovered from the CNS depressant effects and repeated inhalation of solvent was required to maintain the inebriated state. Acetone had a slower onset of effect but was of prolonged duration. Clinical chemistry and histopathological examination of lung, liver, kidney, heart and brain failed to reveal manifestations of acute injury or residual organ damage at time of animal sacrifice. The authors concluded that toluene and

acetone are relatively non-toxic even under conditions of extremely high exposure. However, the usual limitations in extrapolation of animal data to man apply.

The ability of n-hexane and MBK to cause peripheral neuropathy was first recognised in 1969 when Yamamura described polyneuropathy in workers exposed to these solvents. Subsequently neuropathy was reported in such workers (Billmaier et al, 1974; Abbritti et al, 1976), in glue sniffers (Prockop et al, 1974; Shirabe et al, 1974; Goto et al, 1974; Korobin et al, 1975; Towfighi et al, 1976), and following one brief intense exposure to spray paint (Aubuchon et al, 1979). Hexacarbons which are neurotoxic inhibit glyceraldehyde-3-phosphate dehydrogenase, which may be the biochemical site of action and a gamma-diketone spacing in the molecular configuration seems essential (O'Donahue and Krasavage, 1979). Mechanisms of neurotoxicity of 2,5- hexanediol have been reviewed by Cavanah (1981, 1982).

The pathological changes in hexacarbon neuropathy consist of axonal degeneration and segmental demyelination (Spencer and Schaumburg, 1977). Peripheral nerve abnormalities have been studied in greatest detail, but the distal ends of the long CNS fibres are affected in a similar way (Schaumburg and Spencer, 1976; 1978). The CNS damage may be masked clinically by the peripheral nerve effects but may be revealed, as peripheral nerves recover, by residual spasticity. With early withdrawal from n-hexane, neurological complications may be reversible (Paulson and Waylonis, 1976); with full recovery after about four months. Permanent disability has been described following high levels of exposure (Shirabe et al, 1974).

Trichlorethylene affects mainly the liver, kidney (Baer and Kimberg, 1970) and heart (Mee and Wright, 1980) but has been associated with peripheral neuropathy and cranial nerve damage, particularly of the trigeminal and optic nerves (Mitchell and Parsons-Smith, 1969). The reason for this cranial nerve selectivity is unclear.

There is no reliable biochemical marker which may herald the onset of neurological complications in subjects exposed to solvents. Nonspecific cholinesterase (Paulson and Waylonis, 1976) or the brain specific isoenzyme of creatinine kinase, (Jockers-Wreton, 1976) as indicators of neuronal destruction, appear most worthy of further investigation.

This review demonstrates the difficulties encountered in evaluation of long term neuropsychological sequelae of solvent abuse. Difficulties arise because of the nature of the groups studied and the variety of methods used in the field of behavioural toxicity. Individual case studies and animal experiments suggest that although gross permanent neurological damage is probably rare, subtle neuropsychological changes may occur following chronic exposure to solvents. There is a need for well planned critical studies on solvent abusers, with particular emphasis on follow-up.

Discussion

Andersen: Is the nasal ulceration you see in the glue sniffers caused by mechanical damage?

King: I think so. Some of the sniffers put the glue into a bag, if they cannot get a crisp bag they put it into a plastic bag and actually put the bag over their head. Most of the earlier reports of deaths were due to the asphyxia caused by this practice. Some of the children have glue on their mouth and their nose when they come into hospital.

Andersen: And would you say you had an epidemic of glue sniffing in England and Scotland?

King: I think it is very common, but people wonder why it did not happen in the 40s and 50s. It certainly seems to be on the increase, although some paediatricians in London say they never see solvent abuse, whereas we see cases every day. In the casualty department I will have one child brought by the police every day I am on duty.

Pace: As you know there is a correlation between abuse of alcohol by the family and alcohol abuse in an individual but was the family alcohol consumption pattern studied in cases of solvent abuse? Secondly, is there any place for blood toluene analysis in primary care, and are there any other blood tests which are helpful when confronted with suspected solvent abuse?

King: Blood solvent assay is extremely useful and we encourage general practitioners to send blood to us if they think a child has been sniffing. The test only requires one ml of blood and we have an answer within four hours. As for alcohol and glue sniffing, all the children belong to socio-economic group five, and most of the families in that group have a high alcohol intake.

Pace: I wondered whether glue sniffing was a modern, poor man's alcohol abuse?

King: This is certainly what has been found in the United States, where the adolescents start off with glue because it is cheap and easy to obtain. As they get out of glue, they go on to alcohol and some of them progress from these onto hard drugs.

Cherry: I can think of two men we have seen in the last year or two who had very high blood solvent levels with no evidence of sniffing. We wondered if these men were, in fact, unable to metabolise the solvents. How do we distinguish between sniffers and that sort of person?

King: I do not really know but I think it is very difficult.

Jamie: I think it is likely that in a deprived delinquent group one will find neuropsychological deficits in about 60%. This would seem to make it impossible to check whether there is any long term damage from solvents. Perhaps we should ask ourselves if there is any way of doing it in terms of matching for

neuropsychological deficit and then demonstrating specific solvent induced deficits rather than demonstrating general effects?

Goffe: You indicated that toluene was the main solvent abused; did it usually occur in a mixture with other solvents?

King: The solvent in the glue contains about 80% toluene, and the remainder is mainly acetone; I do not know what else it contains.

Baelum: I am very surprised that you use blood toluene levels. We normally consider them to be unstable and fluctuating and I would think it unusual to find toluene in the blood two weeks after the cessation of abuse.

Gompertz: There are several pharmacokinetic components, so measuring blood toluene levels at a later stage you are measuring the component related to adipose tissue deposition.

Baelum: But the half-life of toluene in the blood is only about three to four hours.

King: There is actually a biphasic pattern with blood toluene levels. There is an initial peak which falls as the solvent is taken up by the brain and fatty tissue, and a later peak as it is slowly released again. The point I am making is that you should measure blood levels if you suspect abuse at all even four or five days after exposure. If the result is negative that does not mean they have not been exposed but if it is positive, then you do have evidence for exposure.

9. EPIDEMIOLOGY OF SOLVENT-RELATED NEUROPSYCHIATRIC DISORDERS

O. Axelson

For some time, exposure to solvents has been suspected to cause disturbances in memory, thinking and in affect (cf. Münchinger 1963). A number of recent cross-sectional studies have strengthened this view because of impaired results in psychological tests in groups with exposure to solvents (see Lindstrom, 1973; Blume et al, 1975; Husman et al, 1975; Lindström et al, 1976; Hänninen et al, 1976; Knave et al, 1976; Hane et al, 1977). In experimental human exposure, some impairment in performance has also been oserved, particularly slowing in simple reaction time after an exposure time of a few hours (cf Gamberale 1976). Furthermore, epidemiological studies of men exposed to carbon disulphide have suggested that the behavioural disturbances may be chronic (Hänninen, 1971); there are some clinical observations to support the idea of chronic effects in, for example, styrene workers (cf. Axelson 1975), and a so-called chronic painter's syndrome has also been described (Arlien-Soborg et al 1979).

The cross-sectional studies and clinical observations referred to above, tend to provide an uncertain basis for a more definite judgement as to whether or not there are chronic and irreversible effects from solvent exposure. Exposure to solvents could easily, but erroneously, be blamed for having caused various disorders because exposed and non-exposed individuals might not necessarily be equally well motivated for psychological testing; there could also be a considerable hang-over effect from the last few days of exposure preceeding testing. Moreover, diseased individuals and their relatives generally tend to blame external factors for their poor health.

Some epidemiological studies have also indicated an association between neuropsychiatric disorders and occupations with solvent exposure (Axelson et al, 1976; Mikkelsen, 1980; Olsen and Sabroe, 1980). These studies will be discussed here

in detail and some of the problems involved in this type of epidemiological research will be outlined.

Comments on design and results of studies of neuropsychiatric effects of solvent exposure

The first of these studies (Axelson et al, 1976) used a regional pension fund register as the source of subjects. Since the Swedish social security system encompasses all citizens, this register constituted a complete source of information about all the individuals in the region who had received a pension by reason of disease. Moreover, diagnoses and information about the social circumcstances, years of employment in various occupations and so on were available through the register.

It might be noted that, as a first step, subjects from the register were restricted to include only skilled workers in reasonably well defined occupations. Furthermore, the age limits were set at 35 and 64 years to avoid a dilution effect by young individuals without pertinent exposure, and at the age of 65, a retirement pension is provided. The study period comprised the years 1969 to 1973 inclusive.

Cases were defined as individuals with any type of neuropsychiatric diagnoses except primary debility, schizophrenia or manicdepressive psychosis.

Mental disorders with an obvious organic cause were also not accepted as cases, for example dementia due to traumatic brain injury or encephalitis. Since the diagnoses of cerebral atrophy and presenile dementia might represent the same condition, it seemed reasonable to include cerebral atrophy among the cases. Diagnoses of head-ache of unknown origin or unspecified vertigo were also included as cases.

The referents were all skilled workers on the pension fund register but who were completely free from any kind of mental disorder or social experience which might indicate mental disorder. No person with any type of brain injury was accepted as a referent.

A problem anticipated in the design of the study was that unskilled workers might have been more likely to become candidates for a pension on neuropsychiatric grounds because of some primary mental deficiency, and at the same time, they would not have had the opportunity of being exposed in a skilled occupation such as that of a painter, varnisher or carpet layer. This made it necessary to restrict the source of subjects to encompass only those occupations that had some relation to construction work. Thus, some unskilled and semiskilled occupations and professionals were excluded from the study. To check as far as possible that the relative frequency of solvent-exposed occupations appeared undistorted among the referents by comparison with the source population providing the cases, official statistics and a telephone directory sample were used for comparison, and these gave similar results (Table 9-1).

Alcoholism is a particular problem in studying neuropsychiatric disorders as it causes the same type of injuries that might result from solvent exposure. Therefore, an analysis was made both with and without cases having a diagnosis of alcholism.

Males only were included in the study, and cases and referents were stratified by age to overcome the potential confounding effect when taking years in the occupation as the measure of exposure. The results of the analysis are shown in Table 9-2 and indicate a significant dose-response trend, suggesting an increased risk of neuropsychiatric disorders among painters, varnishers and carpet layers by comparison with other skilled occupations. The same results were obtained when alcholism was excluded from the analysis.

The Danish case-referent study (Olsen and Sabroe, 1980) was based on members of the carpenter/cabinet makers trade union who received disability or early retirement pensions between 1971 and 1975. The case entity in this study was rather broad and included psychoses, neuroses, changes of character, oligophrenias, mental retardation and diseases of the nervous sytem or the sense organs. The referents were equal in number to the cases and were selected from a group of pensioners in the trade union with medical

TABLE 9-1

Percentage distribution of workers in different skilled occupations unadjusted for age.

Occupation	Cases		Referents	Telephone directory sample	Region Örebro[a]
	Alexcoholiseism	Allcoholiseism			
Mechanics Machine fitters Repairers	34.6	29.8	25.9	29.6	29.6[a]
Platers	5.1	5.8	7.0	7.2	7.7
Plumbers	9.0	12.5	4.3	3.6	6.1
Welders	12.8	10.5	9.2	7.2	10.1
Electric and telephone workers	11.5	11.5	11.4	16.2	19.1
Woodworkers	23.0	22.1	30.8	28.9	22.7
Painters Varnishers Carpet layers	(33.3)[c]	(33.7)[c]	(18.9)[d]	(12.7)[c]	(9.3)[c]
Brick layers	3.8	6.7	10.3	4.8	3.3
Concrete workers and similar types of workers	(11.5)[c]	(11.5)[c]	(15.1)[c]	-[d]	(12.8)[c]
Insulation workers	0.0	0.0	0.5	1.2	0.6
Glazers	0.0	0.0	0.5	1.2	0.9
Number of background population	78	104	185	166	13091

[a]Source: Central Bureau of Statistics, Special communication, 1970.

[b]Estimated Value; official statistics seem to include several more occupations than other sources do.

[c]As percentage of other occupations, but excluding painters, varnishers, carpet layers, and concrete workers and similar types of workers.

[d]Exoluded from total number, as concrete workers and similar types of workers were unidentifiable in the telephone directory.

Note: Cases and referents are obtained on a longitudinal basis, whereas the official statistics and the telephone directory sample represent a cross-sectional view.

conditions other than those used to define the cases. From the original 171 cases and referents, 141 and 146 respectively could be located and these subjects were asked to complete a mailed questionnaire; if no longer alive, fellow-workers or trade union officials filled out the questionnaires. The small group of old-age pensioners included 35 cases and a referent group of the same size, 24 from each group being eligible for interview. An employment history suggesting at least 4000 hours of work with organic solvents was used to define the highly exposed subjects. In the analysis, stratification was applied for age, alcohol consumption and history of head trauma and the overall rate ratio was obtained through the Mantel-Haenszel procedure.

A significantly increased rate ratio was obtained from those alive and highly exposed; the ratio was 2.8 (95% confidence interval 1.5-5.2) when considering indoor exposure and 2.1 (95% confidence interval 1.2-3.8) when taking both indoor and outdoor exposure into account. Disregarding degree of exposure, the rate ratios were 1.3 and 1.2 for those receiving a disability pension and an early retirement pension respectively. None of these estimates was statistically significant. Among those with a high exposure, the rate ratio for dementia among those with a disability pension was 2.0 and the rate ratio for neuroses, personality disorders, other non-psychotic mental diseases and mental retardation was 3.1, an overall result which perhaps might be taken to indicate rather imprecise diagnosis within the realm of neuropsychiatric disorders. By using a case entity composed of a variety of neuropsychiatric diseases the rate ratio might be underestimated, a possibility pointed out by the authors. Furthermore, as in the Swedish study, the non-exposed subjects of the Danish study might not be completely unexposed because of the widespread use of solvents, and therefore risk estimates of the study could be somewhat conservative, given a true relationship between solvent exposure and neuropsychiatric disorders since some of the "unexposed" cases might really have been exposed.

The third study (Mikkelsen, 1980) was a cohort study of 2601 male painters and 1790 male brick layers in the Copenhagen area, who were identified retrospectively and followed up from 1971 to 1975. In addition to the comparison of disability pensions in these two groups there was also a reference to the general population of Copenhagen. One hundred and forty three painters and 75 brick layers had been awarded a disability pension in the study period and all the underlying diagnoses had been registered. Moreover, 291 painters and 169 brick layers had died and their death certificates were collected and reviewed. The interest was focussed particularly on the occurrence of presenile dementia, which made it necessary to reclassify the pension diagnosis. The reclassification procedure was not blind but certain steps were taken to minimise observer bias; thus, the word "dementia" or some close equivalent was required in the original diagnosis as well as the term "cerebral atrophy" or some close equivalent. The cases extracted in this way were considered to be one diagnostic group, labelled presenile dementia. Some further sub-division was made, namely with regard to presenile dementia without indication of cause and presenile dementia with indication of cause. The indications of cause in the latter group included infections of the nervous system, head trauma, anoxia, concentration camp syndrome, alcoholism, cerebrovascular accidents, epilepsy and hereditary degenerative diseases.

The only potential confounding variable controlled for in the study was age, and multivariate logit analysis was applied to estimate the risk ratio. The total mortality of the painters was found to be slightly increased by comparison with the brick layers but not with the general population of Copenhagen. An increased risk of disability pension was found to mainly be due to various neuropsychiatric diagnoses. More specifically, the study indicated a risk ratio of presenile dementia without indication of cause to be approximately 3.4 and the risk significantly different from that of both referent groups (brick layers and the general population of Copenhagen). For presenile dementia with indication

of cause, the estimates were 2.1 and 1.7 with regard to the respective comparison groups, neither of which was significant.

Some aspects on validity*

The most serious bias that might operate in epidemiological studies relates to selection mechanisms; if the criteria for the diagnosis include some requirement for exposure, any subsequent evaluation would result in an association between exposure and disease. However, at the time when the Swedish study was undertaken there was hardly any awareness of the possibility that solvent exposure might cause neuropsychiatric disorders. This aspect is of more interest with regard to the Danish studies, however, since there was an increasing awareness around 1974-1975, in Denmark, and elsewhere, of the possibility of solvent-induced disorders. The cases in the Danish cohort study have a rather specific disease reflecting a serious condition which makes it unlikely that there can be any selection effects that would seriously bias the study. The Danish cases in the case-referent study have a broad spectrum of diseases which are unlikely to be subject to any substantial selection bias and would also be expected to make the study rather conservative through a dilution from unrelated conditions. The Swedish Study suffers from including a broad spectrum of disease entity that would tend to make the result somewhat conservative. When the diagnoses were reclassified the result indicated that it was conditions of the dementia type which gave the highest risk ratio (see Axelson et al, 1977).

With regard to the Danish case-referent study based on questionnaires it is reasonable to discuss whether observational bias might have occurred. However, the detailed analyses undertaken in the study reveal a pattern which is unlikely to result entirely from observational problems; the high rate ratios are observed among those with the highest exposure, whereas an observational bias would tend to operate equally for all exposed groups. The Swedish study was based on objective observations of exposure, as obtained from the files of the social security

*see Axelson, 1979

register and the information had been compiled for other purposes and long before there was any idea of a study. Furthermore, the investigators were blind as to the exposure classification of the subjects.

The reference entities in these three studies should also be discussed. In both case-referent studies, non-case subjects on the disability pension register were used to estimate the exposure frequency of the population providing the cases. It is of interest in this context that the Danish cohort study indicated a slight excess of cardiovascular disease (of borderline significance) amongst solvent exposed men and it might be mentioned here that in analysing the Swedish data, cardiovascular disorders were excluded from the referent series, which caused some increase in the rate ratio for the neuropsychiatric disorders although the more conservative estimates (with cardiovascular disorders included) were finally presented in the publication (Axelson et al, 1976). A cardiovascular effect of solvents is possible, therefore, and it seems reasonable to suggest that the indications of an increased risk of neuropsychiatric disorders as obtained in these case-referent studies would be somewhat conservative. Since similar results were obtained in the cohort study both by comparison with the brick layers and the general population of Copenhagen, it seems unlikely that there would be any substantial bias involved in these comparisons with regard to the reference entity.

In all three studies there is a reasonably good control of confounding with regard to age and, as can be seen in Table 9-2, age had little counfounding effect in the Swedish study but merely modified the effect, the quotient of the crude rate ratio to the standardised morbidity ratio being close to one. Considering the rate ratios at different ages, it can be seen that there is a definite effect only in the oldest age group. This is somewhat inconsistent with the experience of the Danish studies, where the effect appears to be evenly distributed over the age range.

Abuse of alcohol might be thought to be a confounder since it can be suggested that some of the neuropsychiatric diagnoses were

TABLE 9-2

Duration of solvent exposure, that is, number of years employed as a painter, varnisher or carpet layer (average 30.7 yr) according to age and with cases of alcoholism included, together with various estimates of rate ratio.

Age	Cases/ Referents	Duration of solvent exposure			
		0	≤30	>30	>0
35-44	Cases	7	2	0	2
	Referents	4	1	0	1
45-54	Cases	28	4	2	6
	Referents	23	3	2	5
55-64	Cases	81	8	19	27
	Referents	186	13	16	29
35-64	Cases	116	14	21	35
	Referents	213	17	18	35
Crude rate ratio		(1.0)	1.5	2.1	1.8
Standard morbidity ratio		(1.9)	1.3	2.2	1.7
Standardized rate ratio[a]		(1.0)	1.3	2.1	1.8
Overall rate ratio (Mantel-Haenszel)					
- point estimate					1.8
- 95% confidence interval					1.1-3.1
$X^2(1)$ Mantel extension					6.7

[a] With the non-exposed as standard

simply unrecognised alcoholism and that the use of alcohol is more common among solvent-exposed individuals than other skilled workers. However, this view would apply mainly to the Swedish study since it is unlikely that there would be any important differences within the single trade union which was the source of subjects in the Danish case-referent study. Moreover, in the context of one of the cross-sectional studies (Hane et al, 1977) investigations were made with regard to painters and other occupational groups registered in the special alcohol abuse register held in Sweden and there was no indication that painters were more apt to abuse alcohol than other skilled workers.

On the occurrence and prognosis of solvent-induced neuropsychiatric disorders

In the light of the results of the results of the three epidemiologial studies that have been reviewed, one might raise the question of the proportion of neuropsychiatric disorders that might be related to solvent exposure. The rate ratios found have been around 2 and consequently the attributable risk among the exposed is about 50 percent; that is, every second solvent-exposed individual with a severe neuropsychiatric disorder might have got this disorder as the result of his exposure. Furthermore, it has been estimated that some 3-4 per cent of all neuropsychiatric disorders causing disability in Sweden might be related to solvent exposure although such estimates are necessarily crude and uncertain. Nevertheless, it seems that the possibility of exposure to solvents should be seriously considered in patients with neuropsychiatric disorders.

To date, several hundred cases of solvent-induced disorders, usually classified as a psycho-organic syndrome, have been diagnosed and compensated as occupational disorders in Sweden. Efforts are also under way to follow these individuals with regard to the course of these disorders, since the prognosis is somewhat unclear. It is usually felt, however, that the interruption of exposure leads to at least a subjective improvement although psychological

function may not improve to any great extent. In a few years however, it should be possible to obtain more definite information on this point.

Considerations for further studies

Judging from the Danish cohort study, and from the reclassification of diagnoses in the Swedish case-referent study (Table 3), presenile dementia seems to be the type of disorder that might be particularly related to solvent exposure. A more specific study should therefore focus on presenile dementia as the case entity. It is noteworthy, however, that a diffuse entity like "nervositas" also gave a relatively high risk ratio in the Swedish study, which might indicate that there can be other effects, or that there are difficulties with making the diagnosis of presenile dementia. There is also the possibility that the physicians would try to avoid the explicit statement of this serious condition in terms of a clearcut diagnosis. Moreover, it is probably necessary to go outside Scandinavia for further studies, since solvent-related conditions attract considerable interest and it is possible that there would be a tendency to make a neuropsychiatric diagnosis when the physician is aware of exposure to solvents. A prospective study should be undertaken based on consecutive cases of presenile dementia, and if possible, computer aided tomography applied in the diagnostic procedure, since it is unclear whether or not cerebral atrophy might also be related to solvent exposure, that is two case entities, presenile dementia and cerebral atrophy should be considered.

Discussion

Lyle: My impression was that you were using alcoholism in the sense of the use of alcohol, rather than as a clinical diagnosis.

TABLE 9-3

Number of subjects with exposure and non-exposure to solvents after reclassification of the diagnoses.

Diagnosis (WHO)		Exposed	Non-exposed	Crude Rate Ratio
Cases				
(290)	Dementia senilis et presenilis	7	17	2.5
(296-297-excl. 196.10; 296.39)	Psychosis affective et status paranoicus (excl. psychosis mano-depr., typus manicus et circularis)	1	5	-
(300-301)	Neurosis (neurasthenia) et persona pathologica	6	34	1.1
(303)	Alcoholismus	9	30	1.8
(309.20)	Perturberationis mentis per laesionem cerebri	2	1	-
(347)	Morbi cerebri alii (atrophia cerebri)	0	5	-
(780.50; 781.70)	Vertigo; Encephalopathia	2	2	-
(790-excl. 709.19)	Nervositas (excluding debilitas)	7	21	2.0
(791.99)	Cephalalgia NUD	1	1	-
(290-791.99)	Neuropsychiatric disorders	35	116	1.8
Referents		35	213	

Axelson: I think both apply. The problem arises in these studies if people use alcohol to such an extent that it causes brain damage but the cause of the damage is not recognised. They are given some neuropsychiatric label which can confound the issue. I might perhaps add with regard to alcoholism that we have registers of alcoholics in Sweden and we checked to see if painters were more frequently registered as alcoholics than other occupational groups but we have not found that to be the case. In another study (Hane, et al, 1977) we had a group of 52 painters whom we compared with 52 other individuals and we found that we had one more of the controls than the exposed registered as an alcoholic. So there is no definite indication that solvent exposed groups use alcohol more than other groups.

Gamberale: Not being an epidemiologist I have some difficulty judging what your risk ratios mean. How large are they compared with those found in other types of study?

Axelson: They are of the order of two, which is not very high in the context of occupational epidemiology generally.

Cherry: I have been trying to translate the risk ratios into some more directly relevant terms. And I think what we are saying is that one in ten solvent workers will have psychiatric treatment which he might not otherwise have had.

Axelson: Not only treatment, but a pension on psychiatric grounds and this is a rather more extreme aspect.

Hernberg: You mentioned that you might have a rather conservative estimate because you have an exposure also among the referent cases. I think that perhaps this error is even greater than one would think because solvent exposure is rather frequent in the population at large. Between 5 and 10% of all workers are

exposed to solvents, at least to some extent, so that some of the so called unexposed workers are actually exposed, increasing the extent of the underestimate. I am not so pessimistic as you are about carrying out further studies in Scandinavia. You could just carry out a retrospective study relying on records, not history. I also think you overestimate that alertness of our colleagues. If somebody is sent to a Clinic of Occupational Diseases then it is likely that his or her diagnosis would not be dementia but rather solvent poisoning.

Axelson: If you looked specifically at dementia I would say you could be right.

Hernberg: We have seen several patients with carbon disulphide poisoning who have dementia and other pathological manifestations, but they all have a diagnosis of carbon disulphide poisoning; they are not registered as anything else.

Cherry: When I read your original paper, I got the impression that it was amongst the rather minor psychiatric symptoms that there was an excess. Is that so?

Axelson: No, I would not say that these are minor symptoms, since they were all sufficiently severe to disable people to the extent that it was considered that they would never work again. There may be some debate about how these conditions should be classified or what the diagnosis should be, but there is little doubt that these individuals had such severe conditions that they could not work.

Carter: What is the natural history of this condition in these people once they have been removed from exposure?

Axelson: That is a question which we are now trying to focus on in Sweden. A cooperative study has been set up between the occupational clinics to follow up all the cases that have been diagnosed as solvent poisoning.

My impression is that the patients improve symptomatically when removed from exposure, but the psychological testing does not improve very much and some continue to decline.

We selected our study group of 52 painters and 52 controls in 1973 and we have them followed up until 1977. It is interesting to see that among the painters there were three deaths but none among the controls, whereas early retirements were the same in both groups, but complaints were still more common among the painters; perhaps this indicates a somewhat poorer prognosis for those with exposure to solvents, although our numbers are very small (Hane et al, 1978). A few of these painters had a particularly poor performance on testing, but at the time of the study we saw no reason to remove them from exposure, but after a couple of years they came out more clearly as cases of mental disorder.

10. EXPOSURE CHAMBER STUDIES

I. Andersen

The purpose of this paper is to review briefly the main studies on human subjects exposed to solvents under controlled conditions in climate chambers, to present some of our own work on solvent exposures, and finally to discuss some problems which have to be considered when exposure chamber studies with solvents are planned and evaluated.

Different types of experimental exposure to solvents

Studies of human subjects exposed under controlled conditions are important, as they allow conclusions to be made about cause-effect relationships. For that reason they are useful supplements to epidemiological studies and to studies in the workplace, both of which are troubled by a multitude of uncontrollable variables.

Exposures of human subjects under controlled conditions to any airborne pollutant may be performed by mouthpiece inhalation, where only the airways are exposed to the pollutant, by "head only" exposures, where the airways, the eyes and the skin of the head are exposed to the pollutant by means of a "diver's helmet" arrangement, and by exposure chamber studies, where the whole body is exposed to the pollutant.

Only the last type of exposure resembles that experienced in the workplace and is to be preferred regardless of the higher complexity and cost of equipment than in the two other types of exposure. As a matter of fact, any exposure study under controlled conditions is expensive because of the extensive technical equipment which is required.

An exposure chamber for studies of airborne pollutants consists of a chamber housing one or several subjects; a technical facility to maintain the basic climatic conditions (temperature, humidity, etc.); a pollution generating and monitoring system, and a data acquisition system for physiological and performance measurements and for subjective responses (statements on degree of eye irritation, fatigue, etc.).

One important drawback to exposure chamber studies is their short duration. To reduce defection, investigations on subjects sampled from the general population normally have to be restricted to the duration of a normal working day - about 8 hours, and the longest exposure period will probably be one week. Only highly dedicated subjects, such as trainees for space travel or deep sea diving may be confined for several months. Therefore, only acute and subacute exposure effects can be studied in exposure chamber experiments.

Exposure chamber studies with solvents

Due to the great number of solvents my review will be restricted to three only, toluene, xylene, and trichloroethylene, all of which are used widely and in great quantities. Further, I have selected from the literature only those studies in which exposure concentrations were not greater than three times the present threshold limit value (TLV) and of at least one hour's duration. The reason for these limitations is that the studies most relevant for the normal daily conditions in the workplace are those of some length and near the TLV.

The human exposure chamber studies with toluene which fulfill these criteria are listed in Table 10-1. Amazingly, this very important and widely used solvent has only been looked at in three studies (von Oettingen et al, 1942; Suzuki, 1973; Ogata et al, 1970). Each used a small number of subjects, the maximum is five, so in total, only 13 subjects have been investigated. Most subjects have been relatively young males with no occupational solvent exposure. The exposure periods have been of a length similar to the working day, and in two of the three studies the composition of the solvent is described. From the last column in the table it appears that no changes occurred in respiration rate, pulse rate or blood pressure, and that no acute neurophysiological effects or subjective responses were found; some subjects reported a moderate fatigue and sleepiness, however.

TABLE 10-1

EXPOSURE CHAMBER STUDIES: TOLUENE ≤ TLV X 3 (TLV 1981 = 100 PPM = 375 MG/M^3)

AUTHOR	YEAR	COUNTRY	SUBJECTS				EXPOSURE PERIOD	CONC. PPM	NEUROPSYCHOLOGICAL EFFECTS
			NO.	AGE	SEX	OCC. SOLV. EXPOS.			
Oettingen et al	1942	US	3	35-53	M	-	8 H	300 100 50 "High Purity"	Fatigue, Muscular Weakness, Impaired Coorindation, RR, PR, BP: NS Moderate fatigue and sleepiness RR, PR, BP: NS
Ogata et al	1970	Japan	4-5	23	M	-	7 H	200 100 Comm, GR.	PR ↓ , BP, RT: NS PR, BP, RT: NS
Suzuki	1973	Japan	5	18-22	M	?	6 H	200	PR ↑ , RR, GSR, EEG, Finger Plethysmography: NS

RR: Respiration Rate PR: Pulse Rate BP: Blood Pressure RT: Reaction Time GSR: Galvanic Skin Reflex

The five human exposure chamber studies carried out with xylene are listed in Table 10-2 (Ogata and Nagao, 1968; Ogata et al, 1970; Savolainen and Linnavuo, 1979; Savolainen et al, 1979; 1980). The total number of subjects studied is 30, all males 20-30 years old and with no previous exposure to solvents. In only two cases is the composition of the solvent given; no studies have been performed below the current TLV. There were no changes in respiration rate, pulse rate or in blood pressure and no subjective complaints. Some acute, but weak neurophysiological effects were found - an increase in body swaytime and in the Santa Ana test, noted especially when excursions were added to the normally stable xylene concentration.

Studies using trichloroethylene are listed in Table 3 (Stewart et al, 1970; Ogata et al, 1971; Salvini et al, 1971; Ettema et al, 1975; Konietzko et al, 1975; Triebig et al, 1976). The studies are similar in design to those referred to above, young males without previous exposure to solvents being studied. The total number of subjects, however, is high, 60 in all with 20 subjects in one experiment (Konietzko et al, 1975). In five of the six studies no statistically significant neurophysiological changes were found, and some of the effects found in the study of Salvini et al (1971), were not noted in the other studies. However, the reports on fatigue, eye and throat irritation are consistent and may, therefore, be real effects.

The general conclusion to be drawn from the human exposure chamber studies on toluene, xylene and trichloroethylene at concentrations below three times the TLV is that only weak neurophysiological and subjective complaints have been demonstrated, and no changes in respiration or circulation could be found. This applies to exposure periods of working-day duration and at the present TLVs.

Do these results give a correct picture of the acute effects of these solvents? Could the results, in view of the small number of subjects in each study, be false negatives, or is the population investigated, young male subjects not previously

TABLE 10-2

EXPOSURE CHAMBER STUDIES: XYLENE ≤ TLV X 3 (TLV 1981 = 100 PPM = 435 MG/M^3)

AUTHOR	YEAR	COUNTRY	SUBJECTS				EXPOSURE PERIOD	CONC. PPM	NEUROPSYCHOLOGICAL
			NO.	AGE	SEX	OCC. SOLV. EXPOS.			
Ogata & Nagao	1958	Japan	5	$\overline{23}$	M	+	7H	200	RT ↑ in 1 of 5
Ogata et al	1970	Japan	4-5	$\overline{23}$	M	+	7H	200 100	PR, BP, RT: NS
Savolainen et al	1979	SF	6	21-17	M	+	6H	100 LAB, GR	Body sway, Santa A Maddox Flicker-Fus No Complaints
Savolainen & Linnavuo	1979	SF	6	24-4	M	+	6H	200) 100) + Excurs.	Body Sway ↑ Body Sway: NS
Savolainen et al	1980	SF	8	24-52	M	+	GH	100 + Excurs. LAB, GR	Body Sway ↑ RT ↑ San Maddox NS, No Comp

exposed to solvents, relevant for the discussion of the effect of solvents on middle-aged or old workers, some of them with a life-long exposure to solvents?

In order to answer these questions we conducted a series of experiments with toluene, from which I can present some preliminary results. For the studies of physiological and psychometric performance and of subjective responses we decided to use the standard methods described in the literature.

Two eight hour exposure studies with toluene

In order to provide a well-controlled environment for human exposure studies with airborne pollutants a new double climate chamber unit has been constructed at the Institute of Hygiene, University of Arhus, Denmark. The chambers are made of stainless steel to avoid contamination from the walls and adsorption of pollutants on to the walls. The floor area of the biggest chamber is $30m^2$, and up to twelve subjects can be housed simultaneously. When extensive use of test equipment is necessary, the number of subjects studied has to be reduced to four at a time. The second chamber is smaller, about one third the size of the big chamber. In occupational studies the normal exposure period of eight hours duration is spent in the big chamber (see Figure 10-1), but if longer study periods are needed, the subjects may relax or sleep in the pollution free environment of the second chamber, so that any concentration pattern can be simulated. In the present study only the big chamber was used, and the subjects were allowed to go home after the eight hours exposure period. The chambers are equipped with air condition systems, pollution generating and measuring systems and a data acquisition system for neuro-physiological measurements and subjective responses.

In the chamber we have studied the effects of toluene on a group of 16 young healthy subjects with no previous exposure to solvents and a group of 43 middle-aged printing trade workers occupationally exposed to solvents and 43 referents of the same age with no previous exposure to solvents. The main aims of the study were to compare the effects of toluene on young and

TABLE 10-3

EXPOSURE CHAMBER STUDIES: TRICHLOROETHYLENE ≤ TLV X 3 (TLV 1981 = 100 PPM = 535 MG/M^3)

AUTHOR	YEAR	COUNTRY	SUBJECTS				EXPOSURE PERIOD	CONC. PPM	NEUROPSYCHOLOGICAL EFFECTS
			NO.	AGE	SEX	OCC. SOLV. EXPOS.			
Ewart et al	1970	US	10				7H	200	Romberg, Man. Dexterity, Coordination and Inspection Tests: NS, Eye and Throat irritation, Fatigue
Ata et al	1971	Japan	5		M		7H	200	Flicker-Fusion, RT: NS
Lvani et al	1971	I	6	20-22	M	+	8H	100	Percept, Test, Wechsler MEM, Scale, Complex Reaction Time, Manual Dexterity All ↓ some eye irritation
Tema et al	1975	NL	12 11	19-27	M	+	2.5H	300 75	Auditivite binary choice, Bourdon Viersma, HR, SA: NS
Nietzko et al	1975	D	20				4H	100	Determination, Steadiness, Reaction Time, Aiming, Tapping: NS, Headache 2/20, Fatigue 3/20
Iebig et al	1976	D	7				6H	100	Comprehensive Psyc. Test Battery: NS

middle-aged previously non-exposed subjects, and to compare the effects of toluene on subjects occupationally exposed to solvents for many years with those of previously non-exposed subjects since it is not known if many years exposure to solvents changes the response to acute exposure. The final analysis is not complete, but some of the main conclusions can be given.

I - A study of young healthy subjects

In this study 16 young healthy subjects in groups of four were exposed to clean air or toluene (spectroscopy grade) under controlled conditions. The conditions were air temperature 22.0 ± 0.3°C, humidity 46% ± 6% RH, air velocity 10-20 cm/sec and a fresh air supply of 420m^3/h equivalent to give 5 air changes per hour. The subjects were all males dressed in all-cotton suits with an air insulation value of 0.7 clo. The subjects were sitting or standing during exposure and no extra physical activity took place. The subjects were in the chamber for eight hours a day on four consecutive days. Each day after an initial acclimatisation period in clean air, the toluene was added slowly, so that either 0, 10, 40 or 100 ppm was maintained during 6 hours. No masking agents were used. The order of the exposure to the four concentrations was determined by a latin square design. The measurements performed were physiological measurements (nasal mucus flow and airways resistance), subjective responses using a questionnaire method (eye and airway irritation, perception of odour, fatigue, etc.) and psychometric performance (Wyon et al, 1980; Andersen et al, 1981). A test battery was composed for psychometric testing and included visual perception, vigilance, psychomotor functions and higher cortical functions; the tests were five choice, rotary pursuit, screw plate, Landolt rings, Bourdon Wiersma, multiplication, sentence comprehension and word memory. Before exposure the subjects were instructed in all the procedures, but no training took place. In the statistical analysis of the results the effect of learning during the experiment was taken into consideration.

There were no effects on nasal mucus flow or airways resistance and only slight eye and airways irritation was reported at any condition. However, the perception of odour was unacceptable for three subjects at 100 ppm. Of the psychometric tests only two changed significantly but in opposite directions. There was a decrease in accuracy (more missed targets) in the five choice test, whereas an improvement was seen in the screw plate test (more nuts and bolts assembled). The subjects felt the tests were more difficult and strenuous at the 100 ppm exposure and headache, dizziness and feeling of intoxication were significantly more often reported. Exposures to 10 and 40 ppm did not result in any adverse effects except for the perception of the toluene odour.

In view of the many complaints at workplaces with toluene exposure at or below 100 ppm we found it amazing, especially in view of the highly controlled conditions, that no strong objective effects could be demonstrated with our psychometric tests. We, therefore, re-analysed the results of the psychometric tests on the assumption that a olinically relevant decrease in any performance is 5%. We arbitrarily said that a 5% increase in, for example, reaction time or in error, was relevant. Allowing for type I and II errors of 5% we calculated the number of subjects necessary to demonstrate this 5% decrease in performance. The results are shown in Table 10-4 from which it can be seen that only for screw plate and reaction time test were the numbers of subjects in our group sufficiently great. For other tests, about 50 subjects would be necessry to demonstrate a 5% change in performance. For two special measurements in the 5 choice test (wrong targets, plate taps) more than 900 subjects would be necessary to demonstrate a significant change.

Thus we must conclude that the use of a broad battery of standard psychometric tests for the measurement of subtle acute changes requires a study population of about 50 subjects. In our study 16 subjects were studied which is a higher number than in other toluene studies (see Table 10-1), but, even so, a negative test

TABLE 10-4

NUMBER OF SUBJECTS REQUIRED FOR A NEUROPSYCHOLOGICAL EXPOSURE CHAMBER STUDY

TEST	No. Obs.	The Necessary No. of Obs. to obtain $\beta = 0.05$ with $\alpha = 0.05$		
		$\delta = \hat{\delta}$	$\delta = \hat{\delta}_L$	$\delta = \hat{\delta}_H$
		N	N	N
Rotary Pursuit	20	70	45	200
Sorew Plate	20	25	15	58
Landolt Rings	20	70	45	200
Bourdon Viersma	20	50	27	120
Multiplication	20	70	50	180
Reaction Time	16	14	8	35
Wrong Target	16	>1000	>1000	>1000
Plate Taps	16	1080	920	1100

A Clinical relevant decrease in performance is 5%

α = Type 1 Error, β = Type 2 Error - Acceptance of the Null Hypothesis even if it is wrong.

result could mean that the null hypothesis has been accepted even if it was wrong. The standard design of exposure chamber experiments with only a few subjects involved, therefore, tends to underestimate the acute effects of solvents (and other pollutants).

We decided after that to carry out a similar study with a larger number of subjects and with a simpler design.

II - A study of printing trade workers and matched controls

In this study, 86 males aged between 29 and 50 years took part, 43 were printing trade workers with, on average, 15 years (range 8 to 25 years) exposure to solvents (workers) and 43 were controls with no occupational exposure to solvents or dust (controls). The printers worked in factories which had been studied extensively two years before this study. The exposure to solvents was about 1/3 of the TLV which for toluene is 100 ppm. Toluene was the substance most often identified and in largest concentrations (Baelum et al, 1982a).

Each pair of subjects was randomised to exposure to either 100 ppm or 0 ppm toluene (spectroscopy grade, no masking agents) for six hours. The exposure took place in the climate chamber used in the first study and each subject was studied once only.

The effects of the exposure on well-being, on performance in psychological tests and on the function of the airways, liver and kidneys were measured. Only the results of the three first-mentioned effects will be described here.

Subjective effects were recorded using linear analogue rating scales, and three questionnaires were completed during the day. The groups exposed to toluene became more tired and sleepy during the day than the unexposed groups and reported more irritation in the eyes and the airways and a greater feeling of intoxication. There were no differences between the printing trade workers and the controls.

The performance in psychological tests was measured using ten different dexterity and perception tests: peg board, screw plate, simulated assembly line, rotary pursuit, track tracing, vigilance clock test, five choice serial reaction, Landolts ring test, a

multiplication test, and a test of colour discrimination. The peg board, the simulated assembly line, the track tracing, the vigilance clock, and the colour discrimination tests were new tests not employed in the first study. They are described in detail elsewhere (Wyon et al, 1980; Baelum et al, 1982b).

Exposure to toluene produced effects in four tests, one manual dexterity test and three tests of perception. In the peg board test, the exposed workers and controls were slower than the non-exposed workers and controls. The overall scores in the vigilance clock test were the same for the exposed and control groups, but the exposed groups made more reactions without a stimulus, which is interpreted as due to increased tension caused by slight effects of the central nervous system.

Results in two tests related to the visual system (Landolts rings and colour discrimination) were impaired in the exposure groups. In the Landolts ring test, the number of faults was increased in the toluene exposed groups, who tended also to take longer for the test.

As expected, the printing trade workers had a much better score in the colour discrimination test than the controls, but the score of both the exposure groups was impaired by comparison with the non-exposed groups. For printers a well trained colour discrimination is essential in their job, and an acute impairment due to solvent inhalation is, therefore, of great practical importance in addition to its theoretical interest. The colour discrimination test was added to the test battery as, during the preliminary field investigations, we heard that the colours blended at the end of the working day often differed from the prototype.

Of the ten psychological tests, the printing trade workers had a better performance than the controls in three, the controls were better in two, while there was no difference in five tests. There was no clearcut difference in the sensitivity to an acute exposure to toluene between the two groups.

The lung volumes and airway resistance were measured using a body plethysmograph. No acute effects were found, but the printers had a slightly higher peripheral resistance (lower MEF 25% VC) than the controls. Nasal ciliary function was measured after the exposure using the skyblue saccharine test; no differences were found between the groups.

The investigation showed that the central nervous system is the organ most sensitive to toluene exposure, and that 100 ppm for six hours gives rise to a small but significant impairment in the performance of tasks relevant for normal work. The effect was seen equally in those with long-term, occupational exposure and those with no previous exposure.

Conclusions

The main conclusions to be drawn from the literature reviewed and from our own studies refer to the general design of the exposure chamber experiments and to the specific effects of toluene.

Few of the studies of solvents in the literature are adequately designed and controlled. The inadequacies relate to the quality and description of the exposure conditions and the experimental procedures, and to the number, age and nature of occupational exposure of the subjects.

The most serious deficiency, however, is the very small number of subjects normally participating in each study. A small number of subjects increases the risk of type 2 errors - acceptance of a null hypothesis even if it is wrong. For future studies it is therefore strongly recommended that the number of subjects should be determined by calculations based upon knowledge about the inter individual variations in the tests used. The intra individual variation including the effect of learning in each test should also be included if the test is used more than once.

Our own studies have shown that it is possible to carry out large-scale experimental studies under controlled conditions using subjects up to 50 years. A combination of young and middle-aged non-exposed subjects with similar groups of occupationally exposed

subjects makes the study design more relevant for occupational medicine. We found that both groups of middle-aged subjects reported more symptoms than the young healthy, non-exposed subjects. The older subjects were also slower and affected in more tests than the young subjects. The lack of total identical design of the two studies makes it difficult to draw clear-cut conclusions.

However, the possibility that many negative findings in previous experiments with solvent exposure could be due to type 2 errors in combination with the extended use of young healthy, previously non-exposed subjects for such studies means that the information gained from the literature on the acute effects of solvents during workday-long exposures at controlled conditions probably underestimates the effects of solvents on workers.

Specifically for toluene we have found in our studies that, in addition to the moderate fatigue and sleepiness reported in the literature, further subjective and objective changes are found after a workday-long exposure at 100 ppm. Headache, dizziness, a feeling of intoxication and perception of toluene odour are adverse effects reported significantly more often at 100 ppm than in clean air. Any psychometrric test is felt more difficult and strenous during the exposure to 100 ppm toluene. In an extensive psychometric test battery, one manual dexterity test (peg board test) was significantly slower, and three tests of perception (vigilance, Landholt rings, and colour discrimination test) were significantly impaired during the exposure condition. These effects are important and interfere with the workers' safety and well-being and deteriorate the quality of the work performed. This speaks in favour of suggesting that the TLV for toluene should be lower than the present 100 ppm.

For future work in chambers we suggest that adequate numbers of relevant subjects are studied; that only spectroscopy grade solvents are used for the exposure to avoid the effects of impurities, and, for the same reason, that no masking agents should be added. Concentrations should be kept constant, and exposures should have a duration of at least six hours at TLV or sub-TLV levels.

Conditions in the chamber should be constant and the physical activity well defined. The exposure should be continuous with meals and toilet facilities provided in the chamber, and there should be a fixed period of training before any test procedure is undertaken. We should like to suggest that a test battery generally agreed upon should be used in each experiment, and to this could be added tests designed to mimic important tasks in the jobs relevant for the pollutant studied. We also suggest that subjects of different ages always should be studied, males as well as females.

Discussion

Herberg: In many of your tests you showed a large learning effect, but in the exposure chamber study you have just carried out you report no change, or a slight improvement. How do you interpret this? Do you think that there actually is an effect?

Andersen: I think there is a type 2 error.

Herberg: My question has nothing to do with statistics. Biologically, how would you interpret your test results, assuming you have enough subjects, if there is no change in the test during an exposure when you would expect an improvement without exposure?

Andersen: The learning effect was included in the statistical analysis. We calculated the learning curve for each subject and used that to look for differences every time there was an exposure. It was an extremely difficult statistical analysis.

Gamberale: You say that you have controlled for the learning effect through the use of a latin square design. This is not to say that you have necessarily eliminated the learning effect which, in these tests increases the variability of the results to such an extent that it will mask small effects due to the solvents. Another point I would like to raise concerns which effects we should be

studying. In the chamber experiments I have done I have been looking for narcotic effects, effects on the level of arousal. Putting lots of people into the same chamber, and allowing them freedom of movement must interfere with measurements of arousal. We have tried to test several people at the same time but were not able to produce a reliable measure of the simplest test of all, the reaction time test. Because of this we have been obliged to limit testing to 2 people and separate them geographically in order to get a reliable measure of reaction time. Looking at the job oriented test you have been using, I am reminded of the work psychology of the 1950s when we were using such tests to select people for a job. But these tests are not very suitable to assess neurotoxic effects.

Andersen: What we are really looking for is an effect at the threshold limit value. We are interested in setting threshold limit values, and therefore we want to have in the climate chamber those conditions which best resemble those found in the workplace. The number of subjects is a matter of balancing choices. If you use the same subjects on several occasions, there is the learning effect to take into account but if you have them only once, you have a very big individual variation. I am not suggesting that our way is the right one, but there should be some agreement about how to perform these experiments for setting threhold limit values. Personally I do not think that we can set future threshold limit values on the basis of controlled studies on a small number of subjects, on a few studies in the workplace and many animal experiments. We will have to do much more extensive controlled studies on human subjects.

Lyle: I think you certainly demonstrated the enormous capacity of the human to adapt rapidly to psychological tests, but I wonder whether one day exposure should be used for setting TLVs?

Andersen: About two thirds of the threshold limit values are set on the basis of irritation, so acute exposures are taken into consideration in those cases.

Lyle: People adapt very rapidly to chemical irritation. Many people go into a factory and find that something in the atmosphere irritates their eye or nose but after a short time they adapt and come to no permanent harm. I would be worried if relatively minor things became absolute guidelines for industrial practice, and I think my concern relates to the small effects noted in behavioural testing.

Gamberale: The question to be asked, is what are we looking for? Are we looking solely for effects on the individual's production or are we trying to determine if a substance is biologically active.

Gompertz: We need to ask both kinds of question, those which are relevant to work and those which are relevant to biological effects; and our battery of tests must be able to ask both.

Howard: We must also ask whether the biological effects are meaningful in real terms. That is the question which is frequently not asked.

11. FIELD STUDIES OF THE ACUTE EFFECTS OF EXPOSURE TO SOLVENTS

F. Gamberale and A. Kjellberg

There is much evidence to show that effects on the nervous system due to occupational exposure to neurotoxic substances can be assessed with the aid of psychometric techniques. Thus, deterioration of performance on tests of various psychological functions has frequently been observed prior to the occurrence of manifest clinical symptoms of any toxic action of the substance (Hänninen, 1971; Gamberale, 1975).

Psychometric tests, or batteries of tests, have mainly been used in experimental or in epidemiological investigations. These methods, however, are now also being used by several clinical laboratories for diagnostic purposes. Undoubtedly the application of performance tests in toxicological investigations has increased our knowledge of the potential noxious action of certain substances on the nervous system. The impairment of the behavioural performance of exposed workers which has been observed in several epidemiological investigations, has shown that occupational exposure to neurotoxic substances may constitute a hazard to health and safety. Consequently, these findings have stressed the need for prevention. However, the behavioural effects observed in epidemiological or clinical investigations are generally of little use when the issue is to decide whether, or to what extent, preventive measures are needed in a specific work environment. Thus, in these types of studies, too little is usually known about the specific environmental conditions which have caused the effects observed.

Experimental studies do not suffer from this shortcoming and they have probably influenced the setting of TLVs for several substances. However, the basic limitation of the experimental approach is that the exposure conditions which can be simulated in an exposure chamber are rarely, if ever, representative of the condition existing in the real work environment. In spite of these problems there is some evidence that the assessment of behavioural changes caused by

toxic substances could be of practical importance with regard to the monitoring and prevention of hazards to health. This evidence comes from investigations carried out at work (Götell et al, 1972; Gamberale et al, 1974; Gamberale et al, 1976; Binaschi et al, 1976; Kjellberg and Strandberg, 1979; Kjellberg et al, 1979; Cherry et al, 1980; Cherry et al, 1981; Anshelm Olson et al, 1981; Anshelm Olson, 1982). A brief review of the main results and characteristics of these investigations is given below to give some idea of the potential of this type of field study. In some of these investigations (Gamberale et al, 1976; Kjellberg and Strandberg, 1979; Kjellberg et al, 1979; Anshelm Olson et al, 1981; Anshelm Olson, 1982) the same reaction time test was employed. Some data from these studies will be described more fully later in the paper, following a presentation of the background leading to the choice of this test and a description of the test itself.

Some Field Investigations of Performance Changes

In the study of Götell and coworkers (1972) the performance on a reaction time test of a group of workers exposed to an average of 150 ppm styrene was compared with that of a referent group of non exposed workers of the same age. The mean reaction time of the exposed workers appeared to be affected both before and after a work day.

One of the studies of Gamberale and coworkers (1974) dealt with a possible acute effect on vigilance due to low-dose exposure to anaesthetic gases. It was found that anaesthetic nurses showed a greater intra individual variability in a reaction time test after work than did age-matched nurses with intensive care duties. No such performance difference could be observed when measurements were carried out before the working day.

In the other study by Gamberale and coworkers (1976), workers from four factories building glass-fibre boats, who were exposed to styrene in concentrations varying between 20 and 120 ppm, were compared with regard to reaction time with age-matched workers from two mechanical industries. The workers exposed to styrene had a

longer reaction time, a greater deterioration of reaction time over time and a greater irregularity of performance on the test than the non exposed workers both before and after a work day. However, these differences between the groups were more pronounced at the end of the work day.

The performance of a group of workers exposed to solvent mixtures in concentrations clearly exceeding the TLVs was studied by Binaschi and coworkers (1976) using a battery of tests. No control group was studied in this investigation. However, the effect of exposure manifested itself in a pronounced deterioration of performance after a work day. This deterioration of performance was observed in spite of the use of tests which in a control condition would have revealed a learning effect.

Kjellberg and coworkers (1979) were able to follow up a group of styrene exposed workers after the closing down of a glass-fibre boat factory. They found that the reaction time of the exposed workers was prolonged compared with that of a control group of non-exposed workers. This effect could still be observed four days after the cessation of exposure. No effect was noticeable 35 days after the cessation of exposure.

Kjellberg and Strandberg (1979) studied the performance of anaesthetic nurses in a reaction time task before and after surgical operations. They were not able to find any performance differences between this group and a group of nurses from an intensive care unit.

In the investigations of Cherry and coworkers (1980, 1981), reaction time was found to be prolonged among styrene exposed workers before the beginning of a work day. They also found that early morning urinary mandelic acid concentrations after two days without exposure correlated with reaction time measured on arrival at work.

In a longitudinal investigation (Anshelm Olson et al, 1981) of workers handling organic solvents and solvent based paints in the production of plastic-coated sheets, reaction time was measured several times during a period of more than two years. The

performance of the workers was found to improve over time as a result of changes in the ventilation system and in the working process, which had brought about a considerable reduction in solvent vapour concentration at the work place.

The effects of exposure to a mixture of organic solvents was also studied by Anshelm Olson (1982) among workers in the paint industry. In this study the exposed group performed less well than the control group on most of the behavioural tests used. The differences were evident for both morning and afternoon measurements. Particularly noticeable was a marked decrease in performance on a reaction time test over the course of the day for the workers exposed to the highest solvent levels.

A common characteristic of the designs adopted in all the investigations referred to above is that performance measures were collected both at the beginning and at the end of a work day. The rationale of this design is based on the underlying assumption that the effect of exposure during the day may manifest itself in an impairment of performance at the end of a work day, with a return to normal levels of performance by the beginning of the following working day, after approximately 16 hours free from exposure. If the action of exposure lasts long enough to bridge the exposure-free period between two consecutive work days, performance should also be negatively affected at the start of a work day. Since this type of field study is based on repeated measurements performed on the same subjects, the behavioural tests used must be as insensitve to learning or training effects as possible. It is therefore not surprising that, with one exception (Binaschi et al, 1976) all the researchers have adopted tests of simple reaction time which satisfy this requirement better than other types of behavioural tests.

When measurements of performance have to be carried out at different times during the day, circadian rhythms may constitute a confounding factor with regard to performance changes which is as important or even more important than learning or motivation. However, it does seem possible to minimise or control the effects

of these confounding factors using operations of experimental control such as the use of an age-matched reference group and a balanced design. This was accomplished in some of the investigations reviewed above using a quasi-experimental study design of which a schematic representation is given in Table 11-1.

As shown in the table, half the workers in the exposed and control groups perform the tests before work the first time and after work the second time, whereas the other half perform the tests after work the first time and before work the second time. Balancing the study in this way, a single analysis of variance for each performance variable is sufficient to test the effects of exposure, of learning and of the circadian rhythm independently of each other and to test the possible effect of the interactions between these factors.

Environmental Control By Means of Reaction Time Testing

Considering the results obtained in the investigations reviewed above, it seems reasonable to regard the assessment of behavioural performance as constituting a potential means for the monitoring and control of exposure to neurotoxic substances in a specific work environment. The detection of working conditions leading to CNS depression would clearly indicate the need for improvements in the hygienic quality of the environment under investigation and would, therefore, be a valuable complement to traditional environmental monitoring. The use of the study design outlined in this paper, or the application of a similar strategy to collect measurements of performance directly at the working site appears to be practicable. Some behavioural tests suitable for this purpose are already available and others can be developed. To be suitable for use in the field a performance test must satisfy a number of requirements: the test must be sensitive, short, reliable, simple to administer, resistant to learning or training effects and, most important, the performance measures obtained must be related to early signs of functional disorders.

A performance test which in the opinion of the authors has been shown to meet these requirements better than any other test known to them is a 10-minute simple reaction time test developed by Lisper and Kjellberg (1972) and used extensively in behavioural toxicology research by our organisation.

A point of departure for the development and use of this test was the work by Buck (1966) in which reaction time was shown to be highly correlated with the probability for a stimulus to be detected. This finding implied that reaction time could be used as a measure of perceptual vigilance, avoiding the time-consuming procedure of traditional vigilance tests. The present test was also strongly influenced by the investigations by Lisper (1969) who demonstrated that the shorter the inter-trial interval a reaction time test has, the greater will be the deterioration of performance over time. Thus a high signal density (16 signals/min) was chosen for the test with inter-trial intervals varying between 2.5 and 5.0 seconds in steps of 0.25 seconds. A random series of 32 inter-trial intervals with an approximately quadratic distribution is repeated five times. The testing is preceded by a one minute training period.

At the beginning, the test was used with acoustic stimuli. However, it was subsequently shown that the test could be used with optic stimuli without its characteristics being changed. Using this test, Lisper and Kjellberg (1972) could demonstrate an adverse effect of only one night of sleep deprivation. Prior to their study it had not been possible to observe any adverse effect of a period of lost sleep as short as this without the use of time-consuming vigilance tests (Naitoh, 1970). The 10-minute SRT test has later been found sensitive to the effects of physical work (Lisper, 1977) alcohol (Blomquist and Hedberg-Sowa, 1976) and of coffeine and diazepam (Lisper et al, 1981). The most comprehensive use of the test, however, has been in the field of behavioural toxicology. Besides its use in the field studies referred to earlier, the test has been adopted in experimental investigations (Anshelm Olson et al, 1982; Gamberale et al, 1976;

Gamberale et al, 1978) and in epidemiological studies (Elofsson et al, 1980; Iregren, 1982; Knave et al, 1978; Knave et al, 1979).

Analysis Of Data From the SRT Test

Six of the field and epidemiological investigations (Anshelm Olson, 1982; Elofsson et al, 1980; Gamberale et al, 1976; Iregren, 1982; Knave et al, 1978; Knave et al, 1979) in which the SRT test has been used have been subjected to detailed statistical analyses by Söderman et al (1982). In total the analyses comprised data from 292 workers occupationally exposed to solvents and 424 non-exposed control cases. This large data base permitted a detailed description of various test characteristics and of the performance changes caused by solvent exposure and increasing age. A further purpose of the analyses was to arrive at a standardised treatment of data.

Figures 11-1 and 11-2 illustrate two fundamental characteristics of the RT performance: the distribution of RT is slightly positively skewed (Figure 11-1) and the RT is gradually prolonged during the ten minutes of the test (Figure 11-2). Both these figures are based on data from the non-exposed subjects.

Figure 11-3 shows the difference between the exposed and non-exposed workers at different points of the distribution. The figure has been constructed by ordering the 160 RTs of each individual from the fastest to the slowest RT.

The mean difference between the two groups at each point of this order was then computed. It is evident from the figure that solvent exposure leads to a general prolonging of the RTs but that this effect is most pronounced in the upper end of the distribution. However, since the variance of the longest RTs is much larger than that of the faster ones, the point of maximum difference does not coincide with the point of maximum sensitivity to the effects of solvents. This is shown by Figure 11-4 which depicts the result of a series of t-tests performed on the ordered RT data. It is clear that the sensitivity is about the same over the whole distribution except for the highest percentiles where it shows a

TABLE 11-1 Experimental design in field studies of acute effects of occupational exposure to neurotoxic substances.

TIME OF MEASUREMENT

BEFORE WORK	AFTER WORK	BEFORE WORK
Eg 1	Eg 1	
	Eg 2	Eg 2
Cg 1	Cg 1	
	Cg 2	Cg 2

Eg 1, Eg 2 Exposed groups
Cg 1, Cg 2 Control groups of age-matched workers

TABLE 11-2 Mean, standard deviation and increase in RT (ms) during the 10-min reaction time test for a solvent exposed group and a reference group of industrial workers with p-values from the analyses of variance of the differences between the groups.

GROUP	$\bar{X}$	s	INCREASE	N
Exposed	282	54	24	292
Reference	270	50	22	424
p-Value	0.000	0.020	0.469	

sharp decline. Figures 11-5 and 11-6 show the results of similar analyses of the age effects on the RT performance. From these and other types of statistical analyses Soderman et al (1982) concluded that the most adequate measures of the RT performance were the mean and standard deviation of the 160 RTs. Table 11-2 presents the means of these parameters in the exposed and non-exposed groups and Table 11-3 gives the corresponding values for the three age groups. One more parameter is accounted for in the tables, namely the increase of the RT during the ten minutes of the test. It is evident from the tables that no effect was observed in this parameter of either solvent exposure or age when the total material was analysed. However, when more homogeneous groups are studied, particularly in repeated measurements designs, this has proved to be an informative variable (Anshelm Olson, 1982; Gamberale et al, 1976).

The balanced design used in the studies where measurements have been made before and after work makes it possible to evaluate learning effects or other effects of the repetition of measurement. There was not the slightest tendency in any of these cases of the first testing affecting the second one (Anshelm Olson, 1982; Gamberale et al, 1975). However, in an experiment where three testings were carried out during four hours a slight but progressive slowing of the SRT was observed (Anshelm Olson et al, 1982).

The stability of the mean RT is also supported by high test-retest correlations. Such correlations have been computed both for field and laboratory data and for testings separated by intervals of varying lengths. With a two hours interval in the laboratory setting the correlations varied between 0.89 and 0.95. For measurements occurring six weeks apart it was 0.75 even though exposure conditions were not the same during the two testings (Anshelm Olson et al, 1982). In the field studies, the testings before and after work have given a correlation of 0.72. This was lowered to 0.56 when a 27 month interval separated the measurements (Söderman et al, 1982).

TABLE 11-3 Mean, standard deviation and increase in RT (ms) during the 10-min reaction time test for three age groups of industrial workers with p-values from the analyses of variance of the differences between the group.

GROUP	$\bar{X}$	s	INCREASE	N
- 35 years	263	45	23	129
36-45 years	270	50	20	97
46-65 years	279	54	23	197
p-Value	0.001	0.001	0.750	

Concluding Remarks

The analyses of data collected with the 10-minute simple SRT test have shown that it fulfils the requirements stated above of an instrument for field studies of neurotoxic effects. The task is short and simple to administer. The measurements have high reliability and the training effects are negligible. Most important, a series of studies of workers exposed to industrial solvents has demonstrated the sensitivity of the test as an indicator of neurotoxic effects. It is true that the differences between the exposed and non-exposed groups shown in the tables and figures based upon the combined material are small. However, this group includes many persons exposed to low levels of solvents. Sub-groups exposed to higher levels show a much larger effect, which thus makes it possible to detect the effects in small groups (e.g. Anshelm Olson, 1982). Furthermore, in an epidemiological study in which the SRT test was included in a large battery of psychometric tests (Elofsson et al, 1980) it proved to be the most sensitive of all the tests used. Of course, both the research strategy and the behavioural test described in this paper have many limitations. However, they constitute a promising point of departure for the development of methods to be used in preventive programmes.

Discussion

O'Hea: When the field studies are carried out, to what extent do you take measurements of other aspects of the environment, for example, the temperature? When a longitudinal study runs over three or four years, do you take account of the time of year? This will affect conditions at the factory. The doors and windows will be open in the summer, thus increasing ventilation. To what extent do you record the ambient conditions in the workplace and include these in the results which you publish.

Gamberale: What you are asking is, if we have been able to control all possible confounding factors? The answer is, we have not been able to do so. But we have recorded the environmental conditions. We have been aware that a difference of one or two degrees Centigrade may affect performance on some tests. When we use the chamber for experiments we can ensure that the conditions are constant but, naturally, we have no such possibilities in the field.

O'Hea: Do you measure and record the local environmental conditions so that they can be referred to at some future date, if they were thought to be relevant.

Gamberale: I have not published that information but it ws recorded and was used in our follow-up study to choose the day to repeat the measurements.

Andersen: You said that the effects on reaction time are reversible, but how long does it take for recovery to be complete?

Gamberale: I do not know. We found an improvement after two years but I do not know if this was complete.

Cherry: We found no improvement in reaction time after a two week break from exposure whereas you found an effect which was reversible after 35 days. The suggestion from that is that improvement takes place somewhere between 14 and 25 days. That is the best information we have at the moment. In the study in which we found an improvement after 14 months we did not know how long that improvement had been there.

MacKay: It is very interesting that in all these different studies of exposure to styrene the unprepared simple reaction test seems to be by far the most sensitive measure. Why do you consider this to be so?

Gamberale: I can only guess. I believe that while solvents have more than one effect, tests of vigilance, like the simple reaction time test, are particularly sensitive to the narcotic effect of the solvents.

Cherry: When we first used the simple reaction time test, the subject was allowed to see his speed of reaction displayed on the machine. When we altered the device so that the subjects did not know how they were doing we got an immediate increase in reaction time, suggesting a motivational effect. Do you think that the results you obtained in your studies are affected by motivation in doing the test?

Gamberale: While I do not think so, motivation has to be taken into account. That is why I am not happy to hear of experiments in which subjects undertake the same psychological tests many times as it must be extremely boring and the effect of boredom may be greater than the solvent effects. We found in testing a large number of subjects on several occasions that there was no appreciable slowing of reaction time due to repeated testing.

12. COMPUTER BASED BEHAVIOURAL TEST BATTERIES

D. Otto

I would like to introduce two projects in which efforts have been made to evolve microprocessor based, portable neurotoxicity testing batteries. The first is the PEARL (Portable Environmental Assessment Research Laboratory) developed at the University of Illinois and focussed primarily on physiological measures. The second, being developed at the University of North Carolina, focusses specifically on the implementation of cognitive tasks, using eight or ten specific sub-processes of cognitive function which can be tested easily using a microprocessor.

The aim has been to produce a screening test that can be taken into the workplace or to a population exposed to environmental pollution. We feel that there is a need to develop tests that can be used to screen populations that may have been exposed to a large number of potential neurotoxins. In order to do this a portable system is required which should be lightweight and modular so that the pieces can be put on an aircraft or into a van and taken to where it is needed. It must be reliable, relatively rugged and simple to operate and maintain. A rapid data aquisition capability is also required since in dealing with screening tests, a large number of subjects may have to be assessed in a short time. With some behavioural measures, such as reaction time, there is not a problem with data storage. With some electrophysiological measures, however, there are about 250 points on each trace; if ten or twelve recordings are made per subject, the problem of data storage is enormous. This is the biggest problem that we have had to face in developing a test battery and we have arrived at a compromise solution by recording the data onto tape. The PEARL system is able to do some on line analysis but for the final analyses the tape is sent to the home base.

The PEARL system consists of a central processing unit with floppy discs. We have not included disc storage in the version

for use in the field as we do not feel that they have the reliability necessary for field testing but we use them for program development and for laboratory work. For electrophysiological recording we have an amplifier system that has to be added on in order to condition the electrophysiological signals that are recorded. For visual tests we have a video screen that can present, for example, a reversing checker board. The subject is interfaced with the system which records his responses to the tests and he may also have electrodes on the arm or scalp to record nerve conduction velocities or EEGs. On the experimenter's side of the system there is a terminal used to start the tests or make some on line measurements as the test proceeds.

The PEARL is a complex system and its complexity may discourage others from proceeding in the direction of automated testing. The Apple system is much simpler with a microprocessor linked to a colour television monitor. The system also incorporates a set of disc drives and a response mechanism which may be a button box although we are experimenting at present with a touch screen. All the information is presented to the subject through headphones. The system is modular and lightweight and can be mounted in a van and taken into the field.

I would like briefly to mention two tests we are incorporating into the Apple system, the Stroop test and the Sternberg memory test. One of the advantages of the Apple computer is that it has excellent graphic capabilities and a colour monitor. In the Stroop test, colour words (red, blue or green) are presented either in the colour they represent or in a different colour. We use only red and blue words. If the word red is presented but coloured blue, the correct response is the blue button. This test has proved very useful in neurophysiological testing and we hope it will also prove useful in neurotoxicity testing.

In the Sternberg memory test, a set of numbers is presented. This is followed by the presentation of a single digit and the subject is asked if it appeared in the previous set. The reaction

time of the response varies systematically with the length of the set of digits, the longer the set, the longer the reaction time. The test can also be performed as a word or pictorial task. In this version, words or pictures are presented one at a time, introducing words that sound alike but are actually different, or synonyms that are actually different words completely. On each successive presentation, the subject is asked to indicate if the word that is displayed is a new word or one that has appeared before.

How useful these tests will be in populations exposed to neurotoxic substances at work remains to be seen but this is a matter to which we much obviously give some attention.

Discussion

Jamie: I have been using the Stroop test, admittedly in a paper version, with a different population and I am getting anomalous results in that the subjects are faster with the confusing colour words than with colour blocks. The subjects were in acute state of recovery from head injury and I suspect that what was happening was that they were demonstrations of an acuity effect. The task becomes rather different under those circumstances and I think that video graphics of colour words might be very prone to this sort of effect.

Otto: When working with microprocessor it is clearly important to know whether any effects are due to methodological artefacts and problems that are caused by displaying stimuli on a video screen. The image tends to be a degraded image even compared with what you would see from a slide presentation. Some experimental video sets are available with finer grain capabilities for presentation so this is one way of solving some of the degradation problems. Other ways of solving the problem lie in more ingenious presentation of the stimulus so that the capabilities of the particular unit you are working with are used to its best advantage.

MacKay: There seem to be problems when using the Stroop test in industry. First, there appears to be a marked learning effect, second, there is a problem of comprehension of the instructions with some of the workforce and third a not insignificant proportion of the population have a colour vision deficit.

Otto: Another problem we are facing now is to design a study on the effects of organo-phosphorus compounds on workers in Egypt. In discussing the battery of tests to use over there we found that only 5% of the workers we were expected to test in Egypt are literate. So any of the

tests that involve verbal mediation cannot be used; this severely limits the kind of test that one can use, and perhaps we will end up going back to very simple tests, like reaction time tests.

Gamberale: Swedish is a very good language for the Stroop test because the names of many colours have three letters, so the test is controlled in this respect. In English, blue is different from red not only because it is a different colour, but also because the length of the word is different; thus you may also be measuring something different from what you suppose you are measuring with the test. I believe you said that your aim was to have a test battery for general use, but I do not believe there is a battery of tests which can be used to investigate every type of problem. Different problems require different tests and different test batteries. I think that tests must be used for specific purposes; I do not believe in tests which can be used in all circumstances.

Otto: I would agree to some extent. But take the example of a chemical dump site. It poses a difficult problem for testing purposes, because even if we take chemical samples we can never identify all the compounds nor their concentrations so we will not know to what the individual is being exposed. It will certainly not be to a single chemical. People who are exposed to a chemical soup are being exposed to an unknown mixture and so what we know about any single ingredient may be useless in determining whether or not the soup has any effect. So how do you proceed to assess exposures of this sort? You must have some test to begin with, since you cannot run a community, whether it is five thousand or forty thousand people through a complete neurological work out; you must proceed with some kind of a screen. We hope to be able to develop some

hierarchical screening strategies, but I do not know how far we are going to get. We need to tackle this problem, however, because if we are faced with another Love Canal, where someone may have to go in to make decisions on how much of the town to evacuate, for example, we shall need to know extensively to assess the individuals, and where to make a cut-off point for a variety of decisions. To do this we need better technology and we think that microprocessor techniques probably are best solution at present.

Gompertz: In the acute situation which you describe you will not be able to match the exposed population with an unexpected group so if you are going to make any valid decisions you will need a huge data base of human behaviour matched on all the relevant factors - age, sex, nutrition, race, occupation; to do this you probably will have to run through about a quarter of a population of United States. I really cannot see then, how you will be able to take decisions based on behavioural testing in the field.

Otto: I feel that some of our electrophysiological measures may be more easily interpreted. We can be more certain if a response is abnormal but that is not to say that it was produced by exposure to agent X. I am not sure that we have the same degree of certainty when dealing with behavioural measures but I see no reason why we cannot develop our techniques to that point; we are not there yet, however.

13. RESEARCH IN BRITAIN

Nicola Cherry, Helen Venables and H.A. Waldron

For some years there has been, in Britain, an active interest in investigating the possible neuropsychological effects of exposure to volatile organic compounds; in 1965, for example, the Printing and Kindred Trades Federation commissioned a study of photogravure workers exposed to toluene, and soon after the establishment of the Employment Medical Advisory Service (EMAS) in 1974, a number of studies were carried out by the Mental Health Branch of men and women exposed to styrene. The upsurge of interest, however, that has led to the present scientific meeting, began at the London School of Hygiene in the autumn of 1978 and has continued, with the support of The Colt Foundation, to provide the chief focus of British research. The work described here was carried out within this programme of work; it should not be overlooked, however, that with the re-establishment of an active mental health branch within EMAS, and the operation of a chamber for controlled experimental exposure at the Health and Safety Executive Laboratories at Cricklewood, there is now the capacity for other British teams to become involved in this work.

The first studies to be carried out at the School of Hygiene were of the immediate and acute effects of solvent exposure during the work shift. These have been described in detail elsewhere (Cherry et al, 1983a): Table 13-1 describes the populations under study.

There were three main findings; (i) that, for all the solvents examined (styrene, methylene chloride and paint solvents), workers exposed to the solvent experienced, during the work shift, a deterioration in feelings of alertness and well being that was greater than that of non-exposed men in similar work; the deterioration amongst exposed men was directly related to blood solvent level, the shift in mood being greatest for those with the highest levels of solvent in a venous blood sample taken at the end of the

Manufacturing Process	Solvent	Range of Exposure (ppm)	Number of Exposed Men	Number of Controls
Glass fibre boats	Styrene	11-191	27 (Mean age = 23.0 years)	27 (Mean age = 26.0 years)
Coach panels from glass fibre	Styrene	6-31	20 (Mean age = 41.6 years)	20 (Mean age = 41.6 years)
Acetate film	Methylene chloride	28-173	56 (Mean age = 43.8 years)	36 (Mean age = 40.9 years)
Paint	1-1-1-Trichloroethane Toluene Xylene	1-46	15 (Mean age = 32.2 years)	*

*Men in this factory were matched with non-exposed men from the acete film factory.

TABLE 13-1. Description of populations involved in the study of the acute effects of organic solvents carried out in Great Britain between 1979 and 1981

working day; (ii) that, on the WAIS digit symbol test (a test of speed and accuracy on a 90 second coding task) exposure levels during the day (as reflected in end of shift blood solvent concentration) related negatively to speed of work; for workers exposed to styrene or to methylene chloride a significant negative correlation was found between blood solvent level and change in rate of work between morning and evening shifts; and (iii) that the start of shift mandelic acid concentration (a urinary metabolite of styrene) was related to score on a test of simple reaction time at the start of the shift.

These initial studies were concerned with the acute effects of solvent exposure on mood and behaviour but also included questions on recent neurological and psychological symptoms (Table 13-2). When the exposed and non-exposed workers are compared it is found that men exposed to solvents are more likely to complain of symptoms although on only two (tiredness and irritability) does the difference reach statistical significance ($p < 0.05$). In one group of workers, however, those exposed to methylene chloride (see Cherry et al, 1981a), an initial study suggested an excess of symptoms, particularly pain and tingling in the limbs, that might be of neurological origin. The excess was greater in those who had been exposed to the solvent for more than ten years. These men were then examined in greater detail, with the aim of detecting any subclinical neuropsychological damage that might be thought to result from long term exposure to the solvent.

No evidence was found for such damage in this group of workers, but the techniques developed allowed us to look for these effects in other groups. The results from two studies are presented here.

In 1980-81, a student at the Institute of Occupational Health, Dr. T. Pace, carried out a survey of symptoms amongst men exposed to paint solvents. He compared the number of symptoms reported on (a) the 16 item Swedish questionnaire (Hane et al, 1980) and (b) the 30 item General Health Questionnaire (Goldberg, 1972), a

	Exposed (N = 108)	Referent (N = 99)	
During the last 12 months have you had:			
Frequent headaches	14	11	
Unusual irritability	25	12	$Chi^2=4.3, P<0.05$
Dizziness	8	6	
Periods of feeling low or depressed	29	20	
Loss of balance	9	4	
Frequent feeling of tiredness or exhaustion	41	18	$Chi^2=9.9, P<0.01$
Numbness or tingling in your hands or feet	14	7	
Difficulty in remembering things	16	10	

TABLE 13-2. Number of men reporting symptoms in the acute studies

measure of current psychological adjustment. His results are shown in Table 13-3. There appears to be a clear excess of 'cases' amongst the exposed men when compared with a referent group of non-exposed men. This suggested that further work should be carried out to see whether there was any evidence of neuropsychological damage from solvent exposure.

A study sample of 60 men was chosen at random from the group of exposed workers taking part in the initial study. Each man was matched on age, educational level, and drinking and smoking habits with a man from the referent group and an attempt was made to elicit the co-operation of the 120 men. Thirty-three men (12 exposed and 21 referents) did not wish to take part. However, all but six of the exposed men who participated were finally matched with a non-exposed worker and forty two matched pairs provided the data for the analysis described here.

In this study each man carried out a series of tests of psychological and intellectual functioning, as well as undergoing a physical and neurological examination and an assessment of his psychological state. Motor and sensory nerve conduction velocities were measured in the median and ulnar nerves and because of a high level of complaint of symptoms that might relate to peripheral nerve damage, an assessment was made of the presence or absence of Raynaud's phenomenon. The results presented here relate only to the performance in the tests of psychological functioning and behaviour.

The tests used have recently been described (Cherry et al, 1982). They comprised a dotting test (see Cherry et al, 1980), the trail making test developed by Reitan (1958), a visual search task (Goldstein et al, 1973), the digit symbol and block design tests from the WAIS (Saville, 1971), the Buschke memory test (Buschke, 1973), a test of manual dexterity (the La Fayette grooved pegboard test) and a test of simple reaction time (Wilkinson and Houghton, 1982). Ability before exposure was estimated by the national adult reading test (NART) (Nelson and O'Connell, 1978).

A. Cases defined by the Swedish Solvent Questionnaire

	Cases	Non-Cases	Total	Estimated prevalence of Cases
Painters	69	174	248	28.4
Referents	15	113	128	11.7
TOTAL	84	287	371	22.6

df = 1, corrected Chi squared = 12.4, $P<0.001$

B. Cases defined by the General Health Questionnaire

Painters	52	191	243	21.4
Referents	16	112	128	12.5
TOTAL	68	303	371	18.3

df = 1, corrected Chi squared = 3.86, $P<0.05$

TABLE 13-3. Cases of psychiatric illness defined by (A) the Swedish Solvent Questionnaire and (B) the 30 Item General Health Questionnaire.

The mean scores on each of these tests is given, for exposed and matched controls in Table 13-4. It will be seen that the exposed men took longer to complete the pegboard test, were slower in the trail making test, did less well in the block design test and were less successful in each of the components of the memory test. They also had a somewhat slower reaction time with more excluded responses (responses greater than 1,000 msec), suggesting poor concentration. It is also apparent, however, that the exposed men, although matched for educational level with their referent, had a lower initial ability, as reflected in the NART score, and in assessing the effect of solvent exposure it is necessary to allow for this.

The second population to be studied was drawn from a factory at which men were exposed to toluene. These men were exposed to more than 200 ppm but had, even in recent years, been exposed to very much higher levels (in excess of 500 ppm) and in early years to even higher levels, at least from time to time. Although the group of greatest interest was that of men with many years exposure, men with less than five years exposure were allowed to take part in the study and 14 did so; men with more than five years exposure were encouraged to do so, and of the 65 men in the group all but 16 agreed to take part in a clinical and behavioural assessment similar to that described above for the men exposed to paint solvents.

The results from the toluene workers and their referents, matched for age and time with the company, are shown in Table 13-5. It will be seen that no substantial difference is found between the groups on any measure considered by itself, although the exposed men do rather worse on 12 of the 17 indices shown in the table, as well as performing less well on the reading test.

It has been suggested that long term exposure to solvents may have a 'neuraesthenic' effect similar to that which may occur in normal ageing, a small decrement then being found in many tests such as those involving memory and concentration, rather than a

		Exposed (N =42)	Referent (N = 42)	P<
Reaction Time				
Mean RT		358.2*	332.2	ns
Excluded respones		0.9*	0.5	
Manual Dexterity				
Pegboard	Preferred hand	74.3*	71.6	ns
	Non-preferred hand	78.8*	73.4	0.05
Dotting test	Lines	31.7*	33.3	ns
	Circles	24.8*	25.5	ns
	Circle errors	0.8	1.2*	ns
Speed of Working and Spatial Ability				
Trail making test	Part A	35.2*	31.7	ns
	Part B	91.4*	80.1	0.05
Visual search	Mean response time	20.8*	18.9	ns
Digit symbol substitution		44.8*	47.2	ns
Block design		34.1*	38.8	0.01
Memory				
Buschke test	Total recall	12.9*	14.6	ns
	Intrusions	5.4*	3.8	0.05
	Long term store	11.4*	13.0	ns
	Retrieval:long term	9.3*	11.3	ns
	short term	3.6*	3.2	ns
Reading Test				
NART		19.7*	26.1	0.001

*Group with poorer performance

TABLE 13-4. Results of behavioural tests in study of painters.

distinct and clear cut inability to perform a particular task (Swedish Work Environment Fund, 1981). If many of the tasks shown in Tables 13-4 and 13-5 have a common factor that is depressed in the exposed men, this could lead to the pattern of poorer results shown in these tables.

The inter-relation of the test scores was investigated by carrying out a principal component analysis of the test scores obtained from the 246 caucasian men (123 exposed and their matched referents) having English as their first language and being included either in the studies of paint solvents and toluene outlined above, or in the initial study of methylene chloride workers (Cherry et al, 1981a). The reading test, reflecting ability before exposure, was not included in the analysis, and the results of the two parts of the trail making test were added together to provide a single score. Thus 16 scores were entered into the component analysis. Weights for the first component, accounting for 32% of the overall variance, are shown in Table 13-6. Examination of these weights suggests that a man who concentrated well and had a good memory would obtain a high positive score. In the digit symbol test, for example, where the man does best if he both memorises the code and operates very quickly, it is (just) possible to complete 90 items in 90 seconds. A man doing so would, when his standardised score is multiplied by the high positive weight associated with this item on the first component, add considerably to his score on the summary factor. A man taking many seconds to complete the pegboard test, however, given the negative weight for this item, would have a large negative component added to his summary score on the first principal component.

The interpretation of the component as reflecting capacities that deteriorate with age was tested by computing a correlation between the individual score on the component and age in the group of unexposed men. A correlation of -0.33 was found, indicating that older men have a lower score on the factor. It remained to

		Exposed (N =59)	Referent (N = 59)	P<
Reaction Time				
Mean RT		325.7	338.1*	ns
Excluded respones		0.5	0.6*	
Manual Dexterity				
Pegboard	Preferred hand	79.6*	75.5	ns
	Non-preferred hand	85.4*	80.2	ns
Dotting test	Lines	35.1	33.7*	ns
	Circles	25.5	24.6*	ns
	Circle errors	2.5*	1.4	0.05
Speed of Working and Spatial Ability				
Trail making test	Part A	35.6	36.9*	ns
	Part B	94.4*	87.0	ns
Visual search	Mean response time	23.8*	22.5	ns
Digit symbol substitution		42.1*	43.7	ns
Block design		30.5*	32.3	ns
Memory				
Buschke test	Total recall	12.8*	13.2	ns
	Intrusions	5.4*	4.2	ns
	Long term store	10.8*	11.3	ns
	Retrieval:long term	8.9*	9.6	ns
	short term	3.8*	3.5	ns
Reading Test				
NART		16.6*	19.6	0.05

*Group with poorer performance

TABLE 13-5. Results of behavioural tests in study of men exposed to toluene

see whether exposure to solvents had any effect on this factor, entering age (which had been matched in each group) as a covariate. For the group of 246 men, a factor reflecting 'exposed or not' was found to be strongly related to the factor ($F=8.1, p<0.01$).

This result provided some support for the hypothesis that exposure to solvents had an effect on capacities that is somewhat akin to effects that may occur with ageing. However, in the studies reported here there was also the problem of differences in pre-exposure ability in the groups exposed to toluene and paint solvents and their referents; having allowed for age, reading scores had a marked effect ($F=37.8, p<0.001$) on the score on the he summary factor. The regression analysis was therefore repeated, for each study population separately, with the effect of solvent exposure being tested after allowance for both age and reading ability. Workers exposed to paint solvents (Table 13-7a) but not those exposed to toluene, were found to have significantly worse scores on the summary factor computed from the first principal component. The size of this effect could be estimated from the regression analysis, exposure to paint solvents apparently producing a decrement in summary score that is approximately equivalent to 11 years (2.70/0.24) ageing. A similar calculation for the men exposed to toluene gave an estimate of 7.8 years ageing, although in this group any apparent effect of exposure was within the range of chance variation.

Were this result for the paint solvents accepted to be a true reflection of the harmful effect of the solvents, the implications might be far reaching. A slowing of capacities equivalent to 11 years of ageing may not be seen as a reasonable or acceptable outcome of work, and there would, at least, seem to be good reason to investigate ways of reducing exposure. There are, however, two problems in interpreting the data. First, there is not the slightest evidence, having allowed for age, that men with many years exposure do worse on this factor than men with few years exposure; this is a rather general finding in cross-sectional

Dotting Test	
Lines	0.46
Circles	0.45
Circle errors	-0.04
Trail Making A and Trail Making B	-0.75
Visual Search	-0.50
Digit Symbol	0.77
Block Design	0.66
Pegboard Test	
Preferred hand	-0.63
Non-preferred hand	-0.60
Buschke Test	
Intrusions	-0.28
Recall	0.63
Long term store	0.69
Retrieval from long term store	0.72
Retrieval from short term store	-0.44
Simple Reaction Time	
Mean	-0.51
Excluded responses	-0.45

A high positive score and a high negative score indicates good function

TABLE 13-6. Weights for first component from component analysis of 16 performance variables.

studies of solvent exposed workers and has been discussed in detail elsewhere (Eloffson et al, 1980). Second, the choice of a referent group, even one matched for educational level, cannot be regarded as in any way satisfactory when the measure of pre-exposure ability, as reflected in the reading test, shows such very marked differences. Statistical adjustment for such differences can only use the scores obtained in the test, and cannot take account of the wide range of underlying abilities which are more or less adequately reflected in such scores. While such a test may indicate, if it is equally distributed in exposed and referent groups, that there is no reason to suppose that the groups are badly matched, some question must always remain about the measuring of the difference in capacities between groups when this initial screening shows matching to be inadequate.

By chance, the exposed men at the docks and the non-exposed men at the toluene factory had distributions of age and ability that were very similar, and it was possible to carry out an individual matching for 34 of the painters against 34 non-exposed workers at the factory in which toluene was used. Such a matching across studies raises problems of population differences and variations in testing procedures that can, to some extent, be overcome when the referent group is employed at the same establishment as the exposed. However, the regression based on this matching provides at least an interesting comparison with Table 13-7a; the estimate of 'years ageing' in this comparison is only 5.6 years, with the importance of the factor representing exposure being greatly reduced (Table 13-7b).

This brief review of recent research in Britain has shown few effects that can unequivocally be attributed to long term exposure to organic solvents. It has, however, made apparent the need for more closely focussed research to answer questions (discussed further in the Preface to this symposium) that were not foreseen at the start of the research programme, but which could now be answered using the facilities and experience of work in this area that have been developed in Britain since 1979.

A. Painters matched with non-exposed referents from the same factory (42 pairs)

	Beta coefficient	F ratio	P<
Reading test	0.13	11.38	0.001
Age in years	-0.24	29.34	0.001
Exposed (=1) or not (=0)	-2.70	7.84	0.01

Estimated years of ageing = -2.70/-0.24 = 11.3 years

B. Painters matched with non-exposed men of equal ability from toluene factory (34 pairs)

	Beta coefficient	F ratio	P<
Reading test	0.15	4.47	0.05
Age in years	-0.18	10.12	0.01
Exposed (=1) or not (=0)	-1.10	1.06	ns

Estimated years of ageing = -1.10/-0.18 = 6.1 years

TABLE 13-7. Estimates of ageing effects of paint solvents.

In his paper, Axelson has underlined the need for further epidemiological work to be carried out in countries where the 'solvent induced psycho-organic syndrome' is not a familiar concept, and where diagnosis is unlikely to be influenced by knowledge of a man's occupational exposure or his eligibility for compensation. For a number of reasons - size of the populations exposed, the level of training of occupational physicians, the degree of union interest and the quality of research techniques that have been developed in the behavioural and psychological sciences - Britain provides an excellent environment, as yet free from diagnostic bias, for such studies that may extend our knowledge of the aetiological role of solvent exposure in psychiatric illness. It is to be hoped that some of the work reported here will provide a basis for future studies that will be of value both internationally and to the unions and managements concerned with the health problems of workers in Britain.

Discussion

Carter: Are the mood changes related to irritation from the solvents? Most speakers have mentioned eye, nose and throat irritation and I wonder if there is any evidence that exposure to non-narcotic irritants such as sulphur dioxide or ammonia causes alteration in mood? In other words, can you separate the solvent effect from the irritant effect?

Cherry: We have done some exposure chamber work with narcotic substances that are not irritants and still find changes in mood.

Jamie: May I comment on the Nelson test? I have found, with an entirely different population, that it may not be as resistant as it is reported to be. People with acute conditions may have extreme difficulty in reading, but this subsequently recovers. It may be that you are being hard on yourself, because the difference may, in fact be a result of solvent exposure.

Cherry: If that is the case, we are being conservative about our conclusions. None of the people we tested was acutely ill nor were there any obvious signs of confusion or acute distress.

Lucas: Did any of the subjects have pyrexia? If they had, their performance, mood and their emotional well being could be impaired; that could be a factor.

Axelson: There may be a difference between exposure to white spirit and exposure to toluene. Painters have told me that they can distinguish between white spirit and toluene and that the experience from toluene is rather pleasant, whereas white spirit produces unpleasant drowsiness. Styrene metabolites are not too dissimilar from the biologically active amines, although lacking the important amine structure. If an amine group were put into the molecule, you would probably have a tremendously stimulating effect. I wonder if, despite

the lack of this amine group, there could still be some stimulating effect? Styrene workers say that when they have a cold they do not get nasal congestion and this reminds me again of preparations that are given to reduce congestion, so there may be properties which can be sympaticomimetic and stimulating.

Gompertz: Was there any correlation between the use of mild tranquilisers between the exposed and non-exposed groups in any of the studies?

Cherry: We had no way of checking this. In one study we did check blood alcohol against reported intake and found a good correlation.

Ekberg: Have you any estimate of how many of the men exposed to high levels of toluene had left the job? Was there a selection effect?

Cherry: There almost certainly will be a selection effect but the toluene factory is the biggest employer in that area and there is little alternative employment so that would tend to keep down the turnover rates, but we do not know much about those who have left.

Gamberale: One prerequisite for the use of psychological tests is that people will work at their maximum capacity. Fluctuation in motivation could produce differences in results. Is there any possibility that motivation differs between Scandinavian and British workers? In Scandinavia people will generally follow instructions and you can be relatively certain that they will work as hard as they can.

Cherry: I am sure there are going to be cultural differences in the way people view their health and in how they work on tests. I would not be happy if cross-cultural differences were found on computer testing, because there you can do nothing about motivation. In the studies where you have one man and one tester, and the tester is going out of her way to get the best out of

the subject you will tend to get an optimal performance. We have aimed to get people working at their peak capacity because of this problem of differential motivation between exposed and non-exposed workers.

Goffe: There could have been a difference in the motivation between the subjects and the controls in the toluene study because in that case the study was initiated by the trade unions. The counter argument to that is that there is high unemployment in the area; there is a great deal of job insecurity and everybody is highly motivated to keep their job. So there could be a number of different problems affecting motivation.

O'Hea: Were smoking habits recorded, and if so, is it possible to differentiate between the results of smokers and non smokers.

Cherry: We have done that and there are no differences.

Ekberg: You said that the control group in the docks study had a higher educational level. What effect would that have on the results?

Cherry: You can stratify the sample by educational level and look at the results separately. But amongst those who left school with no qualifications, the control group have a higher reading score; this suggests that stratifying just by educational level may not tell you enough about performance capacity before exposure.

14. DISCUSSANTS

1. PSYCHIATRIC VIEWPOINT

E.G. Lucas

From the psychiatric point of view the differential diagnosis of minor degrees of confusion, impaired intellectual function, depression, anxiety and overall impaired performance is of great importance. Apparently, changes in performance and behaviour are the two presenting symptoms which cause most concern in the workplace. They may result appropriately in the individual presenting to the personnel department, the occupational health department and ultimately to a psychiatrist. It is most important to review the whole human being, taking into account the emotional and physical environment, including noise and toxic substances in the atmosphere. Medically prescribed, illicit drug and solvent abuse are also relevant. The issue is, how many background data are relevant when considering the significance of possible occupational toxic exposure? Coincidental physical illness must also be included. An objective assessment of previous personality, any underlying psychiatric morbidity, pattern of alcohol consumption, head injury at work or elsewhere must all be reviewed before attributing deterioration in performance to industrial toxic exposure. A potentially useful objective account of the individual is available when work performance is routinely appraised. Domestic behaviour and adjustment are relevant to work and acceptable liaison between the General Practioner (Primary Care) and occupational health department is useful provided appropriate confidentiality is preserved. In addition to prescribed drugs, sleep disturbance and night sedation, the use of stimulants such as excessive coffee intake may also affect performance.

In clinical psychiatry, it would be helpful to have a package capable of screening for potentially toxic substances when dealing with a patient who presents with an acute psychotic or confusional crisis. Apart from acute psychiatric clinics, differential diagnosis in accident and emergency departments would be facilitated.

The whole area of clinical behavioural toxicology does seem to merit much more study. During discussions we often become concerned by the nature of presenile dementia, including its histopathology, pathophysiology and biochemistry. In this symposium I do not think we should be too concerned with semantics. Suffice to say that in the workplace, pre-senile dementia could be responsible for impaired intellectual performance. If solvents age men exposed to them by ten years, as Dr. Cherry has suggested, this has profund implications. Finally, we must decide on the importance of the non-specific symptoms which have been described to us. The neurological deficits of impaired position and vibration sense are posterior column signs and are not only stressful but may also cause the individual to function less well. Thus, anything that causes a group of symptoms that reflect an impaired intellectual, sensory or motor function however mildly, is of great importance. It is necessary to look for ways in which the substances thought to cause these effects can be monitored occupationally and clinically.

Discussion

Cherry: Professor Axelson showed us epidemiological data that suggested that the rate of severe psychiatric illnesses was twice as high in solvent workers as in non-solvent workers. This seems to be one issue that has to be faced, for if one in ten workers are having unnecessary psychiatric admissions to hospital this is a serious matter. The second issue I would like discussed is whether the degree of organic deficit which has been discussed is an acceptable burden, even if it is reversible.

Lucas: One problem arises with nomenclature. Even though there are a few reversible dementias, the current use of the term implies an irreversible, although sometimes arrestable process. Therefore, where intellectual function has deteriorated as the result of solvent exposure, clarification is required as to the subsequent course of impairment following cessation or reduction of such exposure.

Cavanagh: I always think in terms of individual chemical substances whereas we seem to be discussing solvents in general. I am at a loss to know whether we have to think of general neurological effects or of specific effects such as those produced by n-hexane, for example.

Cherry: We are at a bit of a loss too, because although we know what paints are used in the docks, for example, and we know that sometimes the men are exposed to very high levels we cannot identify particular solvents which are producing the effects we seem to find. One possibility would be to get a sample of the painters to record their symptoms every day and relate this to the solvents they used to see whether they are worse with some than with others.

Pace: The whole thing is confusing and I think we are dealing with three different conditions. We have the acute response to the toxic effects of specific chemicals that presents as a well defined clinical pattern. We have the chronic response that we are investigating by looking at different chemicals, and we have a third condition where we are looking at a mixture of solvents and, here, we are in the dark. If, when we talk about the effects of solvents, we talk about all three conditions together, this leads to confusion.

The discussion of presenile dementia was thought to be one of semantics but I think there is more to it. The consensus seemed to be that none of Scandinavian cases would be considered as cases of presenile dementia in this country. Thus, there is a tendency for this work to be unjustifiably and unnecessarily discredited and there is then a risk of ignoring a real effect because we are confusing our terminology.

Cavanagh: You can get presenile dementia from all sorts of causes. It can be caused by Alzheimer's disease, which is a specific process or Pick's disease, or by

nutritional deficiencies or by vascular disease. There are presumably other things which will give a global decay of the cerebral hemispheres and cause a deterioration in intellectual capacity before the age of sixty. But certain people consider that presenile dementia is something concerned only with Alzheimer's disease and I think that is a mistake.

Axelson: I do not think one should focus too much interest on how these cases are labelled. The epidemiologist aims to study the occurance of the disorders that physicians believe are there in the population. I have noticed that there is some difference in terminology between Britain and Scandinavia. When we speak about presenile dementia we tend to infer a vascular cause or repeated infarct syndrome, for example. Alzheimer's disease I think would be classified as an atrophy although it might go unrecognised for some time. I think one should emphasise here that we do not believe that it is the Alzheimer type of disease that is induced by solvents, but that there is a mental deterioration which we have named presenile dementia. But I admit that we might have to change that description for reasons of clarity.

Lucas: May we ask Professor Cavanagh what are the essential pathological criteria by which the diagnosis of Alzheimer's disease is made?

Cavanagh: The diagnosis is made on the finding of stainable structures within the cerebral neurones, or on finding specific changes with the electron microscope. As you know, there is a tendency to postulate lesions in different parts of the hemispheres to account for the symptoms that indicate to the psychiatrist that Alzheimer's disease or Pick's disease is present.

Lucas: May I again stress that alcohol is a common cause of intellectual and physical deterioration and the people

who are exposed to solvents at work may simultaneously be exposing themselves excessively to this very potent toxic substance. This has to be taken into account in parallel with industrial exposures at the workplace.

Goffe: I am not enthusiastic about the concept of solvents accelerating ageing even though it is perhaps more understandable than other mechanisms we have been talking about. I would not be against it if the evidence were unequivocal, but I think we are still on somewhat shaky grounds when we are talking about intellectual impairment. And one other point, it is possible for people with hydrocephalus and marked cerebral atrophy to have a high IQ, so I think one should not be too obsessed by CAT scan findings and the size of people's ventricles.

Waldron: The most crucial work for us now is to perform follow up studies to see whether these deteriorations are reversible or irreversible. If they are reversible, then it is premature to talk about an ageing effect since this is clearly irreversible. From the practical point of view it is important to know the natural history of the solvent induced changes, so that we can give a prognosis to those in whom we find them. It would be comforting to be able to assure patients that they would improve once they were removed from exposure.

Cherry: I think we really have got to get these results into perspective. None of the men we saw at either the toluene factory or the docks had presenile dementia. They were slightly more anxious than non-exposed men and they did marginally worse on the tests. There was no dose response relationship in the sense that the people who had been there the longest were not worse than those who had been there a short time.

Jamie: Working with people with known brain damage one knows that they can recover dramatically even from major trauma, but that deficits appear in later life. It is possible perhaps, that solvents cause trivial brain damage for which the worker is able to compensate. He is unable to recover from the damage in a sense that there is physical repair so that in later life, these deficits show up like the tide going out. And that might be the synthesis between the British work, or the work in the exposure chamber seeing what the immediate effects are, and the Scandinavian work that looks at the pension register which shows up a high incidence of psychiatric morbidity. Maybe these are people, who had you seen them twenty years ago, would have appeared normal, but now that their brains are that much older, the deficits that they acquired slowly and insidiously begin to show up. If that is the case, it would be very difficult to demonstrate.

Axelson: Exactly this question was brought up at a recent conference in Stockholm. There was some agreement that exposure at an early age might well be compensated, but that the disability would manifest itself in later life, perhaps as the result of further exposure. The question of solvent effects in later life is important and perhaps, when doing exposure chamber studies it would be more instructive to use old people as subjects rather than students. Moreover, if you take these patients away from exposure they seem to recover subjectively, to some extent at least, but if you expose them again they seem to be extremely sensitive. They often tell you, I visited my old workmates at the workplace where I used to be employed, and I immediately got the symptoms back again.

Lucas: Of course one could include the psychological effect of knowing they are returning to what they regard as a hazardous workplace.

Ekberg: They do not have to return to the workplace, they also experience the symptoms if they smell the solvent, or something similar to it.

2. STATISTICAL VIEWPOINT

D. Oakes

I would like to start with the meaning of statistical significance since we have had p values presented at the symposium from time to time. The point I would like to make goes back to R.A. Fisher (1966) who wrote, "In relation to the test of significance, we may say that a phenomenon is experimentally demonstrable when we know how to conduct an experiment which will rarely fail to give us a statistically significant result." Thus in interpreting significance levels we must consider, not just whether the p is less than 0.05, but all the other aspects of the study, which would allow us to question whether if repeated many times, the study would continue to give a p value less than 0.05. That issue involves both the design of the study and the amount of analysis to which the data have been subjected.

It would be wrong to talk about epidemiology here without mentioning Sir Austin Bradford Hill (1977) and his famous criteria for causality. I have been trying to keep a check list on some of these points. In terms of the strength of association, we seem to be seeing relative risk or rate ratios of between two and three which are not in themselves strong enough to rule out the possibility of other explanations through confounding factors. The relationship in time was mentioned previously and I think we are short of information as to whether the supposed cause always preceeds the supposed effect. We need more studies that are longitudinal in nature and that take measures before people are exposed to the substances in question and continue to follow them up; of course subjects should be followed up after cessation of exposure as well as during exposure. Concerning dose-response one of the most striking features of the studies reported is that much effort has gone into ascertaining the response, but very little into ascertaining the actual exposure of individuals. This may be extremely difficult, particularly in the epidemiological studies or the long term studies of chronic effects.

There is a need, however, to look harder at the aspect of dose, not only in terms of the duration of employment, as some studies have, but also at the concentrations of a particular solvent. We heard very early on that interactions are important and I know that it is rare to find a population exposed to only one solvent. Nevertheless, I think, one has to look for such populations and having identified them, one has to find out who among them is heavily exposed and who is lightly exposed. We need to persuade the hygienists to give estimates of which jobs were heavily exposed in the past, not necessarily in absolute terms, but at least in terms of relativities. We have heard of one or two studies in which there has been some defined end point such as a disability pension. I will not address the issue of possible biases in that; that has been discussed already, but I do want to make the point that the exposure classification from a census or from a register, where the person may be described as a painter or a bricklayer, is in itself very crude and it would be desirable to go back to those studies and find out what the levels of exposure actually were. This could be done by carrying out a case referent study within the cohort (Mantel, 1973). By this means you can concentrate on the relatively small number of cases, and a larger but still fairly small number of controls, between five and eight per case has been suggested (Breslow and Crowley, 1981). Having defined the group of cases and controls, you go back and try to construct work histories for them all, ascertaining whether within the group there is any relationship between different levels of exposure and outcome. With a rare outcome this is still much less work than ascertaining exposure for the entire population.

Now I would like to consider some of the described experiments which are, I think, particularly important. They should be designed in such a way that they meld with the epidemiological studies wherever possible, that is, they should be carried out on subjects who are the same type of people as those exposed in the workplace, indeed they may be the same subjects. The experiment has to be planned to take proper account of all relevant sources

of variation, although in practice this is difficult to achieve. The latin square design is elegant. It controls for variations between subjects and for a learning effect which is uniform over subjects. It does not control for a learning effect which differs among individuals. So, if the learning effect is important, and if it is likely to vary between subjects, as it almost certainly will, the latin square design will not help very much and perhaps we should be thinking of different designs. It is possible to put another layer of classification into the latin square, and look at interactions between two different substances. In the statistical analysis, it is important that variability between subjects should be the essential benchmark as to whether or not there is a real effect. Technically, subject effects should be treated as random effects in an analysis of variance table. The reason is that one presumably wishes to generalise the findings beyond the particular subjects under test to the population from which they are drawn. Findings which apply only to some subjects, however exemplary, would not necessarily be of general interest. In the analysis of variance, the main effects of solvents should be tested against solvent by subject interactions, not against the residual mean square obtained from measurement error. So the denominator of the F ratio is the line determined in the analysis of variance table corresponding to the interaction of the solvent with subjects (Green and Tukey, 1960).

Discussion

Gompertz: You talk about subjects being randomly distributed, and I have heard people during the last two days talk about people on the tail. I think it should be recognised that recent pharmacological research has shown that there may be a bimodal distribution with respect to the oxidation at a carbon atom, of drugs and foreign compounds. This means that if you are dealing with small numbers, and there is a ten percent subgroup, you must be aware of the possibility of getting aberrant results because some subjects are

metabolically different from the others. One other point; just as the populations we study are not homogeneous, neither are the solvents necessarily homogeneous. They often contain stabilisers and other additives and it may be that it is the additives not the solvents which are behaviourally active. This needs further consideration.

Carter: I think you will find that white spirit is a straight distillate of hydrocarbons, toluene will be a high purity of hydrocarbon, whereas styrene may contain a polymerisation inhibitor. A number of the chlorinated hydrocarbons do contain inhibitors; commercial trichlorethylene used to contain epichlorhydrin. This may be a problem with some of the chlorinated solvents but not with toluene and not with white spirit.

Cherry: The point about special sensitivity raises some methodological problems. No-one had produced any evidence for it as an explanation of the lack of dose-response relationship. With the exception of Professor Axelson's epidemiological study I cannot think of a solvent study has shown that the longer the exposure, the worse the symptoms.

Axelson: An important issue I would like to discuss is the meaning of dose and exposure in this context. Do we mean intermittent peak exposures as opposed to continuous low grade exposure; and which of these is the most deleterious? And how should we classify exposure? Should it be the product of concentration and time similar to that used to define fibre-years for asbestos exposure or working level months for radiation workers, or should we have some other sort of measure of exposure? Should exposure be weighted so that we take into particular consideration exposure that is remote from the appearance of the disease, or is the most recent exposure the most important? I would say that remote exposure should be taken into account in cancer studies,

but in solvent studies I would consider that recent exposure is more important. I would be glad to hear your comments on this question.

Waldron: What is usually done in this country is to refer, where possible, to a time weighted average. Exposure data are usually inadequate even for recent exposure and this is why reference is seldom made to them. It is unusual to find a solvent industry in which data exist for either general or personal sampling; an exception to this is the toluene factory we have looked at recently where background and personal sampling has been carried out regularly for at least ten years. In this factory we are able to categorise the subjects into exposure groups from the most heavily to the most lightly exposed. We have not yet carried out the analysis, but if within those groups there was no association between the level of exposure and test performance results, I would think that we would have to look for some explanation other than solvent exposure. It is too easy to fall back on the concept of individual susceptibility in the absence of a dose response effect; it is the epidemiologist's last refuge and, like Dr. Cherry, I am waiting to see some good evidence that individual susceptibility to solvents really does exist. There are real problems in using the product of concentration and time to define exposure since this disguises the peaks and troughs and it may be that very high exposures for a short time are more injurious than continuous exposure, even to relatively high levels. But I cannot see how one can do much in historical terms except to say that those men were heavily exposed, these were intermediately exposed and these had no exposure at all; even with this relatively crude grouping, however, you would expect to find some relationship between exposure and effects.

Oakes: I think even if that was all that could be done it would be extremely useful, but I do not recall that anything presented in these two days has actually done that. Provided that the classification is carried out blind as to outcome, then the actual levels of exposure are of secondary importance, provided the relativites are right.

Cherry: That is true, assuming that we are looking at chronic effects, but if all the effects are acute effects which recover when people are removed from exposure, then it is the level to which they have been exposed in the last months that matter. The fact they were exposed to 2000 ppm five years ago is of no consequence, but their exposure to 300 ppm last month may be crucial.

Axelson: Do I understand that you think in terms of level of exposure rather than duration, or do you think that both have to be combined?

Waldron: Exposure is normally presented in terms of a concentration/time product but you always have to bear in mind that you may well be disguising important effects. I do not see how fluctuations in exposure can be allowed for.

Gompertz: In fact it may not be necessary, it all depends on the pharmacokinetics of the solvent. A lot of short term changes are damped by biotransformation. The level of damping will depend upon the speed of metabolism, but it will progressively increase as the compound moves down the metabolic pathway. I would like to have explained to me, the sort of industrial processes that result in intermittent high exposures; this is a rather unusual form of exposure I would think.

Waldron: There are many circumstances under which solvent workers get intermittent high exposure; opening closed systems without using protective masks - this is a regular occurrence. Painting or spraying under poorly ventilated conditions may also produce extremely high exposures. We have seen many examples in our visits to factories.

Gamberale: Are the chances of underestimating exposure larger than those of overestimating exposure? This seems to follow from what has been said.

Waldron: Exposure is probably underestimated, because of the intermittent high peaks and because men do not wear protective equipment on all occasions when they should. If you ask the hygienist to assess a particular job he may well give it a lower rating than it deserves because he makes his judgement assuming the best possible conditions prevail. I think that the tendency, therefore, is always to underestimate, rather than to overestimate exposure.

Gompertz: Our hygiene colleagues at Cricklewood set up a system in which glass fibre boats were built in a workshop monitored with continuous MIRAN sampling. With the tube sampling from the breathing zone they found extremely high exposure peaks. But these peaks would have been damped by the biological system. If we had had an indwelling intravenous catheter, I am sure we would have that blood concentrations would have remained constant. If you look at exposure chamber studies that have measured wash out curves you will find that the biological system reacts more slowly than the environment, and that there are no biological peaks and troughs corresponding to rapid fluctuations in exposure.

Otto: Have any of the studies actually looked at age factor as the main factor? The effect of some toxic substances seems to be accentuated in the older population and it would seem of some interest to assess the effects of solvents on people of different ages.

Cherry: In Professor Axelson's study it was only in the older age group that there was any effect.

Goffe: To go back to exposure, I understand that measuring atmospheric levels is not a good indicator of exposure because a number of other factors, for example work rates ought to be taken into account. Should we not then be

thinking in terms of biological measures rather than atmospheric sampling.

Waldron: I agree, I would always go for biological monitoring where possible because it is the man you are interested in, not the environment. In practice, however, it is usually easier to measure atmospheric levels.

Axelson: I would like to speculate a little further on the question of peak exposures which particularly might lead to solvents or their metabolites penetrating the blood liquid membranes, such as the blood brain barrier. If such structures are affected by solvents I wonder what the consequences would be in terms of leakage of other substances across the membrane. Could the present of solvents allow other materials more easily to penetrate into the brain?

Cohr: We also see that solvents disorganise membranes, especially the long chain hydrocarbons because they are very like the lipophilic ends of the fatty acids that make up membranes. There is a tendency for potassium to leak from the red cells in solvent exposed workers which indicates that the red cell membrane is not functioning as well as it should. And that means that other substances, which would normally not do so, may penetrate into the cell.

Lyle: It is fortunate that this does not happen to any great degree in inhalational anesthesia where enormous doses of solvents are used.

Cohr: The reason that anaesthetic gases do not disorganise cell membrane is that they are very small molecules.

3. PSYCHOLOGICAL VIEWPOINT

A. Summerfield

As someone without a vested interest in this issue, perhaps I could state my conclusions having listened to this symposium. It seems to me that there is a fair convergence of evidence that there are some adverse effects of some solvents; in saying this I am aware that we must remember that solvents are not an homogenous groups of chemicals, and that they may have different consequences at different times. On the other hand, I do not consider that there are any strong implications for immediate action to be taken to reduce exposures through legislation. These are my general opinions as a scientist.

My remit is to discuss the psychological aspects of the problems that have been raised here; given the efforts that have been made, it is clearly difficult to establish strong psychological effects for any of the solvents. The starting point for believing such effcts exist are the reports of symptoms, and one question of importance to psychologists is, "Are the reports of symptoms reliable?" If so, this leads on to the first of the fundamental questions, "Are there long term consequences for health and for mental health?" And that leads to the question, "Are there short term psychological consequences?" I put the questions in that way, because if short term psychological consequences can be demonstrated, then it becomes more worthwhile to look for long term consequences. It also seems worthwhile, as an issue secondary to looking for long term effects, to see if there is evidence of lowered performance, or an increased accident rate at work, or if there are poorer interpersonal relations amongst those exposed to solvents.

On the question of reliability of symptoms, we have had some evidence at this meeting that men who report symptoms on one occasion do so on future occasions, and that it is the men

complaining of numbness and tingling, for example, who have slower nerve conduction velocities. As to long term psychological consequences, these seem to me to remain somewhat controversial. There is evidence for recovery, or compensation in some way, as a consequence of removal from exposure but the epidemiological evidence does seem equivocal. This brings me to the short term effects of exposure to these chemicals which come down to the evidence we have from performance tests. First, we have evidence that, in some contexts, there are well established effects on reaction time, and secondly, there is some evidence of changes in performance on the digit symbol substitution test. If I have abstracted too little from the evidence that has been presented, I am sure I shall be corrected.

There are rather wider questions that I should like to pose about the use of psychological tests. First, why use psychological performance tests at all? I have answered that already, because if there are demonstrable effects on psychological performance, that carries the implication that there are central nervous system consequences that are worth following up. The more important question is, are the right tests of psychological performance being used? What does one mean by the right test? At one level, any psychological test that shows an effect is the right test, in the sense that I have just been arguing, because it does have the consequence that it is worth looking further. But there remains the question of whether psychological tests should be orientated towards aspects of work performance and so be seen to be more relevant to occupational exposures.

Looking at the whole field of performance testing in relation to stressors at low levels, there are at least three sorts of psychological tests that seem to be sensitive. The first is the basic measure of reaction time; here tasks in which the rate of performing is imposed on the person, the so-called paced tasks, have often been shown to be more sensitive to the effects of

stressors or low doses of pollutants than the unpaced reaction time tasks. Vigilance tasks are the second type of test that have been shown to be sensitive; there has been some reference to both these types of test in this symposium. A further type is a somewhat more complex task, where the subject is required to try to do two things at once; in this type of task some division of attention is required and there is some element of competition between the jobs that have to be done.

Psychological tasks of this sort are all rather difficult to take into the field, and that is a powerful reason for avoiding them if it is possible to make use of simpler, reliable procedures. One of the advantages of the use of microprocessors, however, is that they can deliver these more complex tasks to subjects in the field and can carry out the preliminary analyses to give results in a short time. So I should like to provoke you again with a suggestion that microprocessor procedures, especially in relation to psychological tests, enlarge the possibilities of using the complex tasks that may turn out to be the right tests for detecting the sorts of effects we have been discussing at this meeting.

Discussion

Gamberale: I would not like to give the impression that I am against the use of microprocessors. Quite the opposite. For instance, in our chamber experiments we use computerised batteries of tests and I am proposing to take a microcomputer into the field to look for the effects of exhaust fumes from cars. What I am against is developing tests without knowing exactly what the tests are going to be used for. I do not believe that it is possible to use the same psychological tests under all conditions. I like to choose my tests depending on the problem at hand, rather than having the same set of tests to use regardless of the application.

Summerfield: It does seem to me that there is an issue over trying to match psychological procedures to problems. It has been argued that a set of psychological procedures ought to include something that is relevant to the work and the worker concerned and I put it to you that there are varying degrees of difficulty over that. It is one thing to make use of a colour matching test for a printer but what are you going to do for a boat builder?

O'Hea: Could it be that with the advent of the microcomputer, tests could be developed whereby a sample of the workforce, or even the entire workforce could sit at the computer, say ten minutes once a week and have, for example, their reaction time measured so we could tell whether they are taking in harmful amounts of solvents.

Summerfield: My opinion on this is it would be very nice to be able to do that, but we would have first to establish a very strong relation indeed between the change in performance and the levels of chemical in the blood, and I do not think that we are at all close to being able to do that.

Otto: One thing that has impressed me listening to the presentations, is how some of the very basic, simple tasks (such as the reaction time task) have turned out to be the most sensitive. I think we need to develop test batteries which include both the basic tests that have given such a tremendous return over along period of time, and those which allow more complex testing.

The question of having workers sit down once a week and do a test raises a new set of issues that have not been addressed in my work nor I suspect, by many others. You would have to take into account the training, the learning and the effects of doing a given task over and over again. There is a lot of work going

into developing tasks that are impervious to temporal effects, which would be very useful for that purpose. One would have to think through very carefully the implications of such a procedure and I am sure it has probably as many disadvantages as it has advantages, but I think it is a good idea.

Gompertz: I think that it would not be acceptable either to the legislators or the unions to use what may be an adverse effect for monitoring the exposure of the workforce. We ought to have a system of monitoring that prevents workers from being exposed to solvent levels which have an adverse effect. It is not appropriate to measure a decrement in performance as a check on atmospheric levels. We need to set a control limit for the atmosphere that would prevent the worker showing a measurable adverse effect.

Summerfield: Appropros of learning, and memory, it has always seemed to me that from the point of view of cognitive psychology, what is involved in a digit symbol substitution is not straightforward, and certainly involves elements of short term memory even if one rather discounts the initial practice effects. There was question earlier as to whether the suppression of a practice effect is an effect. I am certain that psychologists would have no problem at all in considering suppression of practice as an effect. And there is a scope there for further exploration.

Jamie: I think that the discussion that was published between Kendrick and Rabbit (1982) on the way you should assess the elderly is particularly germaine to computer testing; the effectiveness of the procedure will depend on whether computers are part of the ecology of the

patients' lives. A second point which I sense is getting lost at times, is that the measures that are used to look at the effects of solvents must be validated outside the field of solvent research. I picked up a feeling that there are some who would feel that only measures that do in fact demonstrate a solvent effect are good measures, whereas you really want measures that you know validate against some external criterion, and having listened to the discussions for the last two days I wonder whether there is an external criterion for solvent damage? It does not seem that there is a neuroanatomical one, and I think that one has to go and look at tests validated on the neuropsychological effects seen in brain damaged populations.

Summerfield: Or validated against other stressors, for instance.

Jamie: It is no use taking your microprocessor off with a battery of tests and only selecting those that do show differences between exposed and non-exposed populations.

Summerfield: The point I was making on that, and I would insist on it, is that if you do reliably demonstrate an effect, and it is repeatable in the Fisherian sense, then you do have a datum which makes it worthwhile to go on looking.

15. CONCLUDING REMARKS

H.A. Waldron

It would be impossible to sum up our deliberations in a few words but I would like to make a few personal comments. This symposium has had the substantial benefit of airing this problem for the first time in a comprehensive way in this country, and we have been extremely fortunate to have so many colleagues from overseas to help us. The indications for behaviour effects do seem to be pointing in the same direction, but a lot more work needs to be done to satisfy the decision makers, or the policy makers that the time is right for setting exposure levels on the basis of the findings we have reported here.

It has been a great pleasure to have our colleagues from industry with us. They are concentrating at the sharp end, everything that we do is translated into some sort of written communication which will be read eventually by someone in industry and it is the industrial medical officer who will most often be asked for an explanation. I am not sure how helpful we have been in advising them what the best interpretation of these results is for their workers, but I hope that they have gained something of value from the meeting. Inded, I hope that everyone will take away something of value from the symposium. For those of us who are going to stay here it will be a great sorrow to see you all go, because it has been a most enjoyable two days. One of the original definitions of a symposium was that it was an occasion when one sat down and talked, drank and ate with friends and we have certainly all done that; the social side of this symposium has been a great success and I hope that it will not be too long before at least some of us meet in some other pleasant part of the world to continue our discussions. Thank you all very much for coming and for contributing so much to our understanding of this problem.

LEGENDS FOR FIGURES

Figure 2-1 Distribution and evolution of some of the cranial nerve changes in Case 4 of Buxton and Hayward (1967) which emphasise both the slow advance of the pathological changes and their remarkable spread through the medullary centres.

Figure 2-2 Conversion of trichloroethylene to dichloroacetylene which may be the proximate toxic agent (Henschler et al, 1970).

Figure 2-3 Ulnar nerves from rats chronically intoxicated with CS_2. Note swelling and thinning of the myelin sheath in the proximal paranodal region. This is maximal in a and least in c; b is a normal fibre for comparison. The arrows point distally. Teased OsO_4 stained fibres x 859.

Figure 2-4 Ulnar nerve with one greatly swollen axon and thinned myelin sheath. Note the mitochondria clumped together in the middle of the axon which is distended with filaments. x 1600.

Figure 2-5 Medulla of rat chronically intoxicated with CS_2. Note the greatly enlarged axons containing scattered mitochondria. x 1300.

Figure 2-6 Diagram to show the distribution of swollen axons in various regions of the CNS. The numbers indicate the particular localities affected. (From Cavanagh and Bennetts, 1981.)

Figure 4-1 Diagram of the brainstem auditory evoked potential (BAEP) in an adult. Regions of the brain where each component originates are indicated below the waveform.

Figure 4-2 Pattern-reversal evoked potential (PREP) elicited by stimulating left and right eyes of a patient with multiple sclerosis. Abnormal P100 latency is manifest in this case by interocular asymetry rather than absolute prolongation of latency. The longer latency in the right eye indicates subclinical right optic neuritis despite normal vision and ophthalmological examination. (Adapted from Stockard et al, 1979, p 194.)

Figure 4-3 Procedure to measure central and peripheral conduction times in somatosensory pathways following median nerve stimulation. Peripheral conduction time is measured as the latency of the potential at Erb's point, central conduction time as the difference in latency between the N20 peak (cortex) and the N14 (neck) peak. (Adapted from Eisen and Odusote, 1980.)

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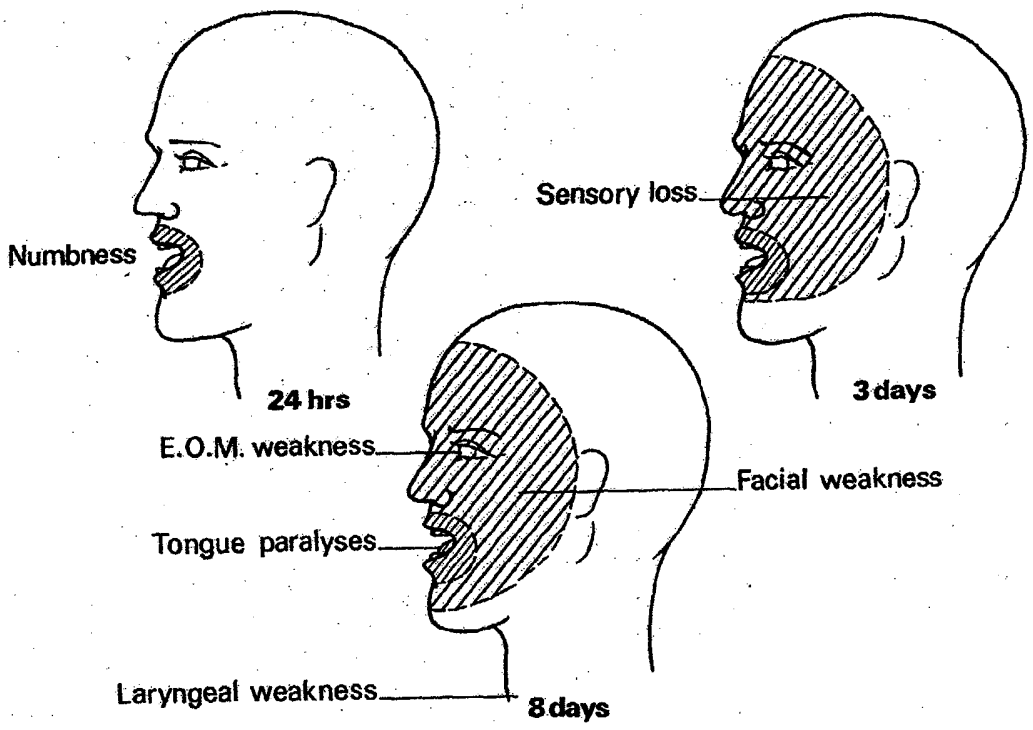

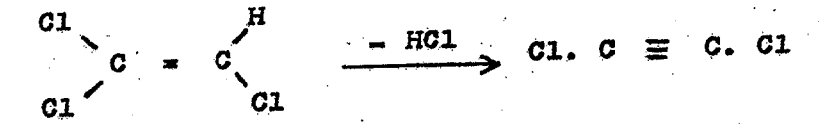

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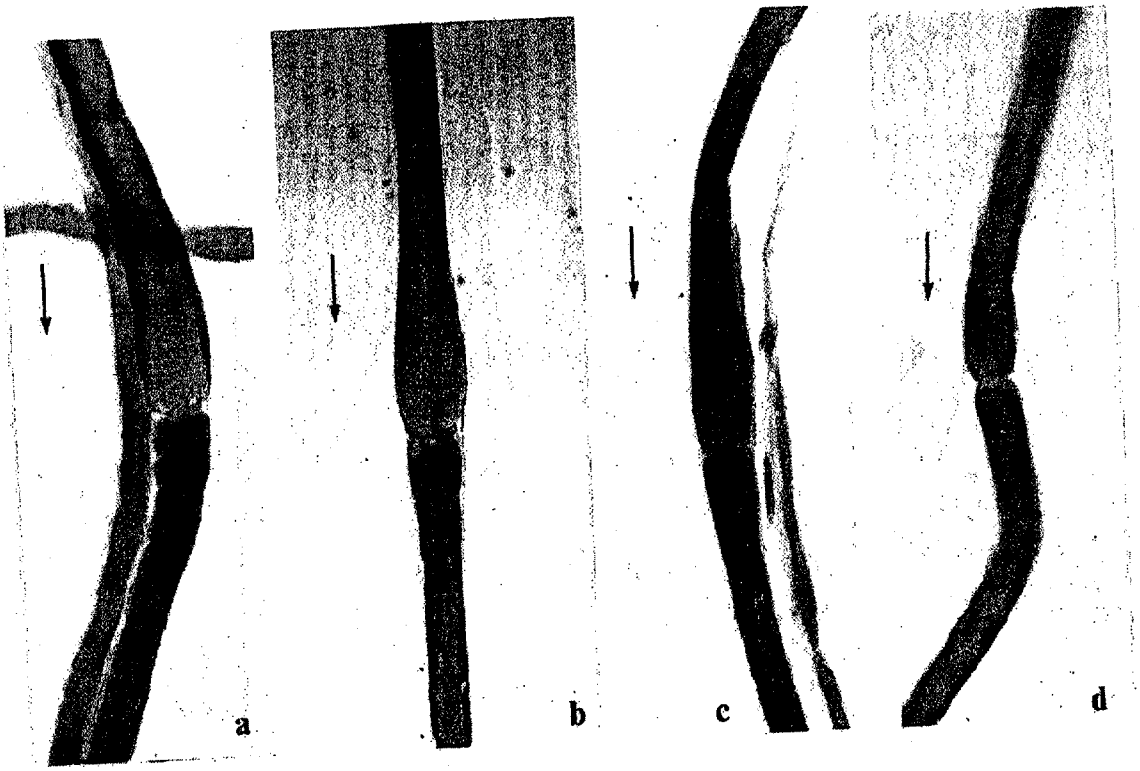
Dichloroacetylene



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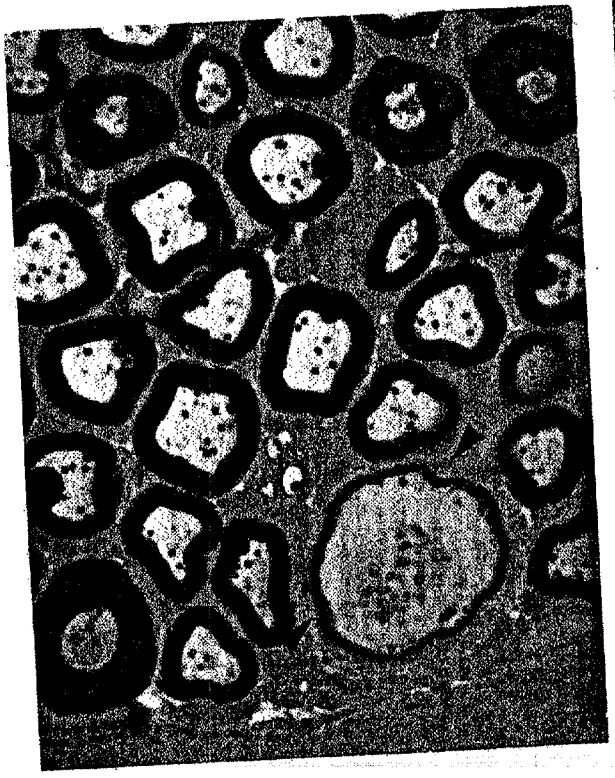

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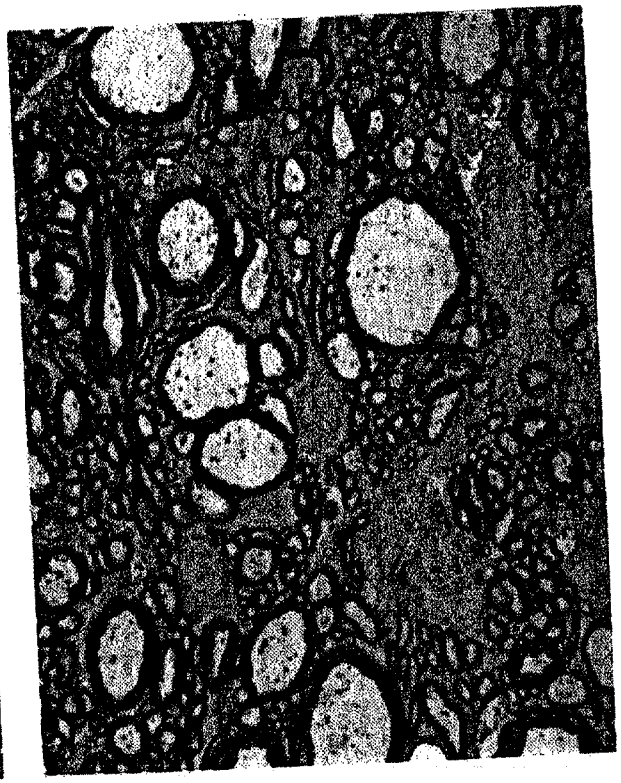

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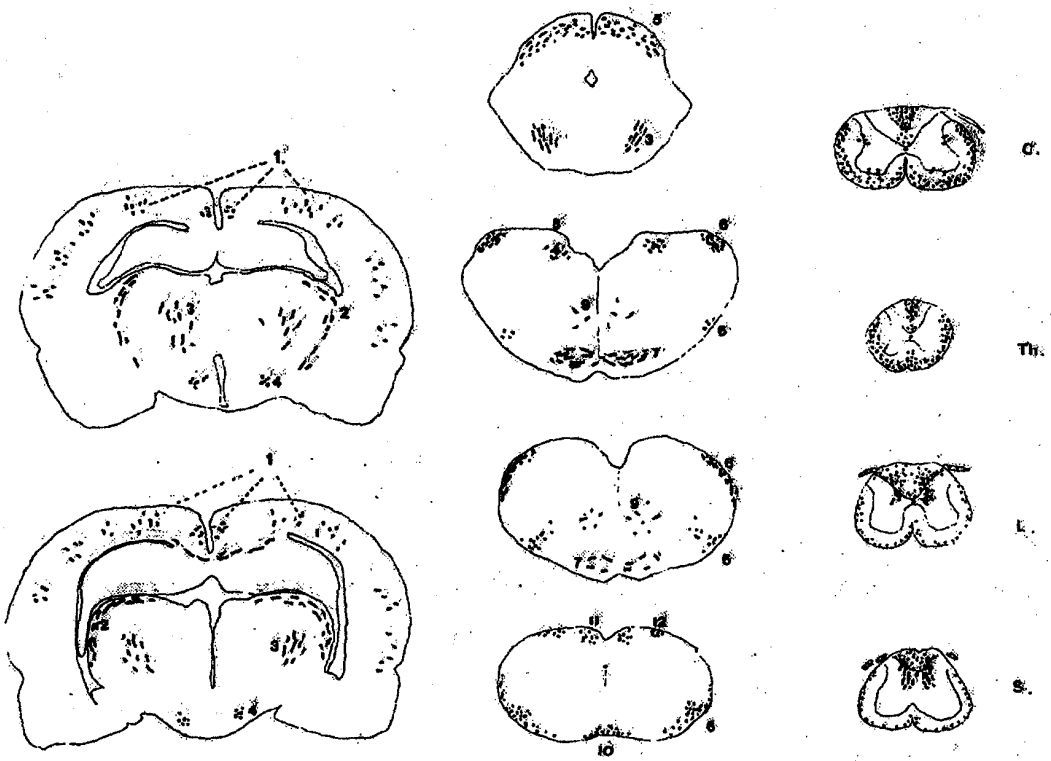

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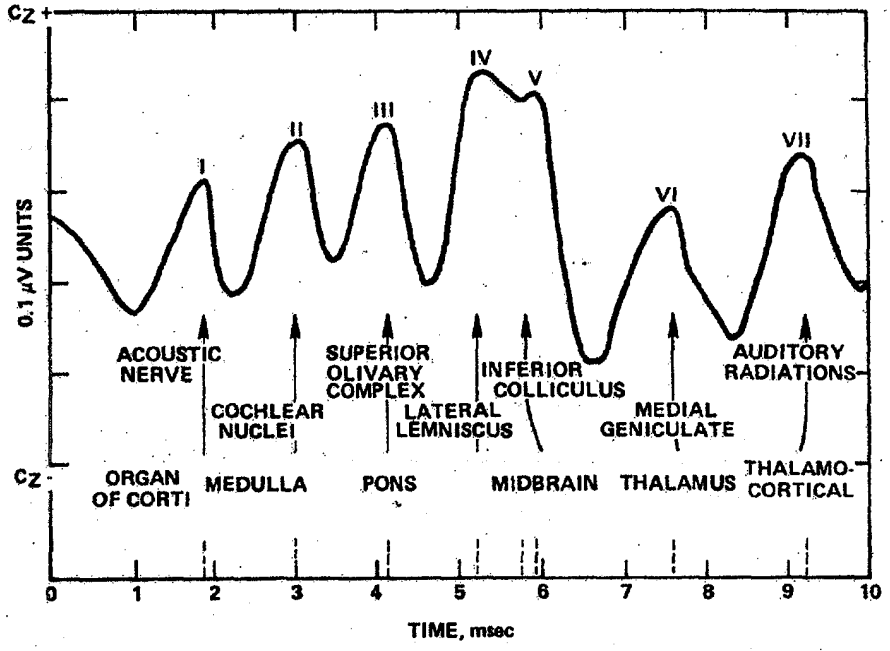

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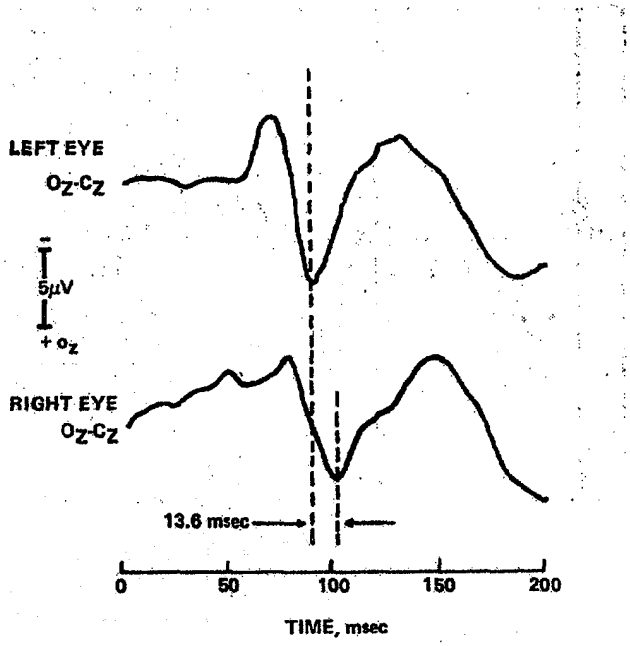

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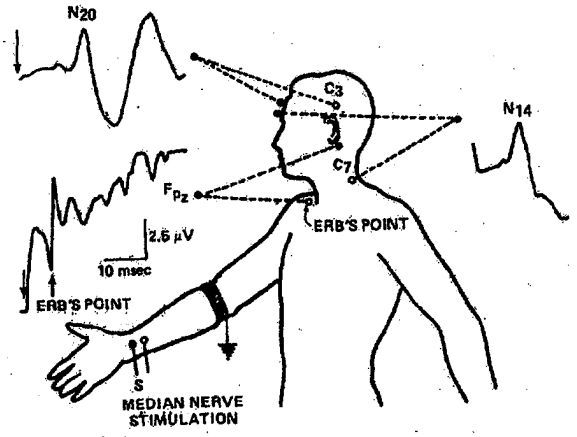

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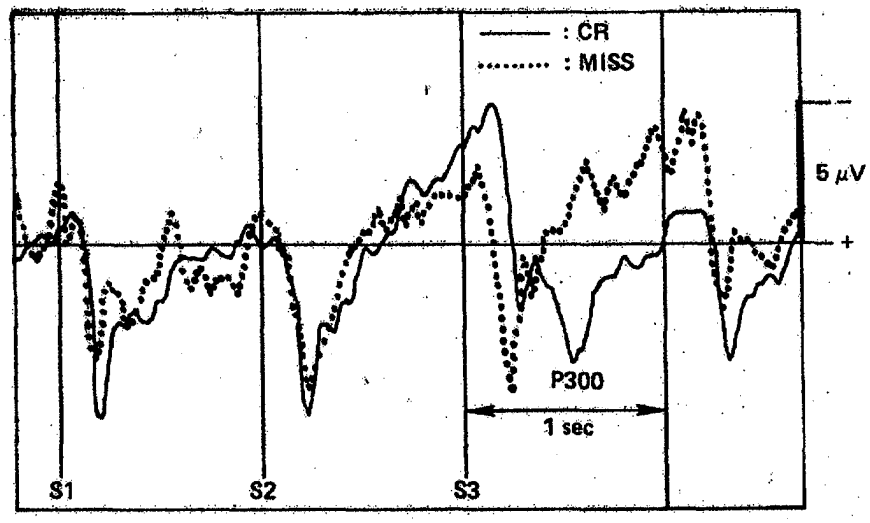

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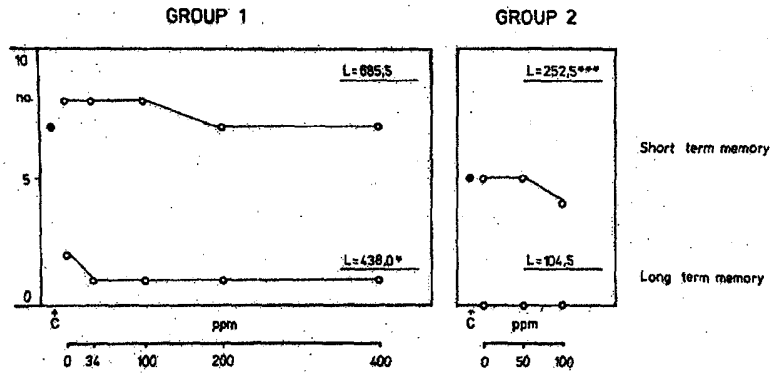

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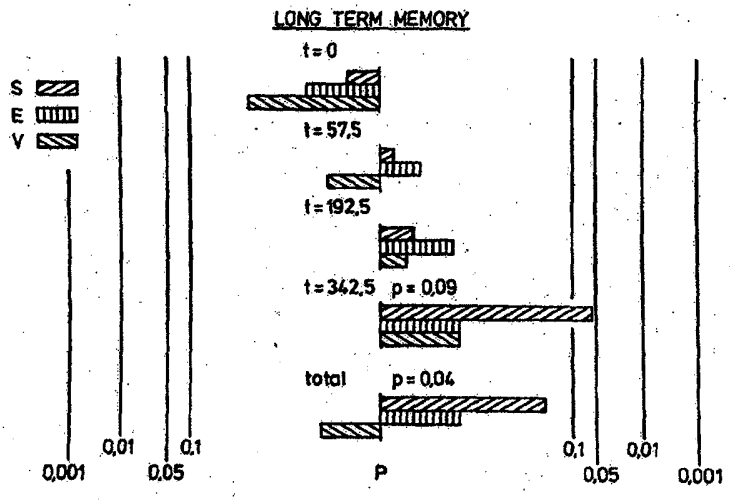

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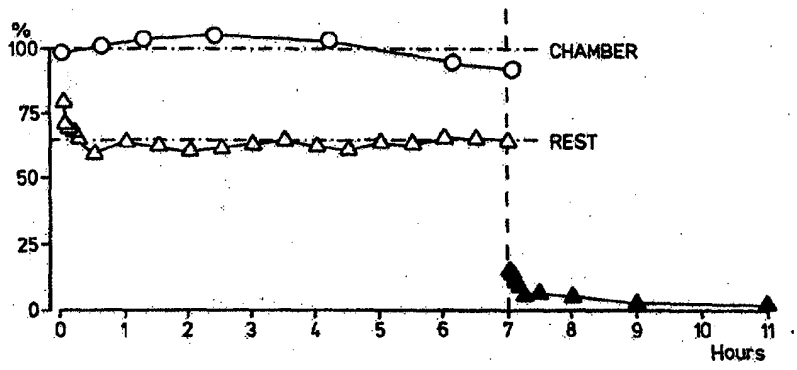
RELATIVE UPTAKE OF ALIPHATICS

FROM THE INHALED AIR



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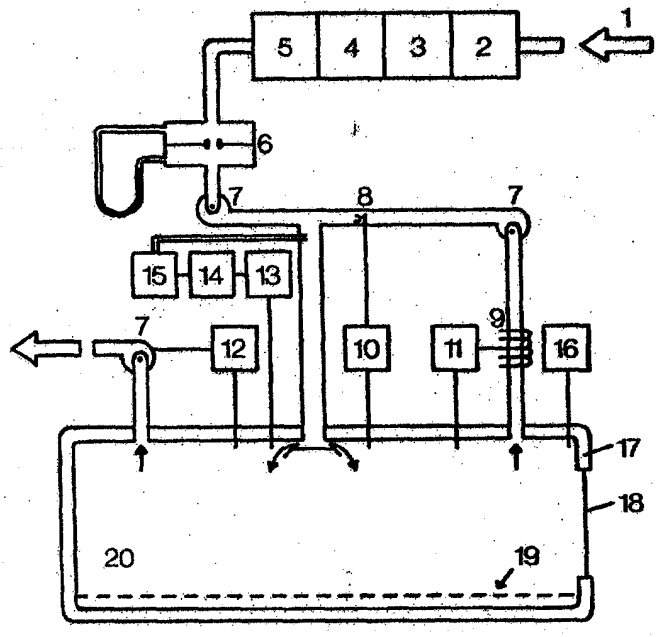

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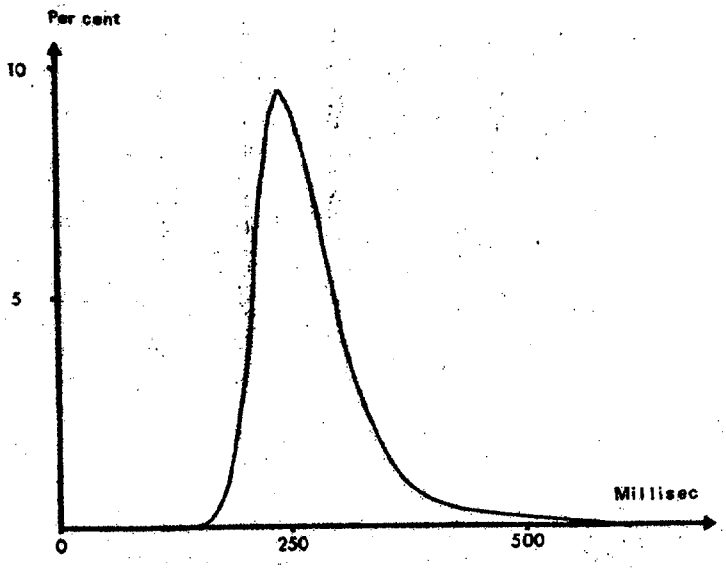

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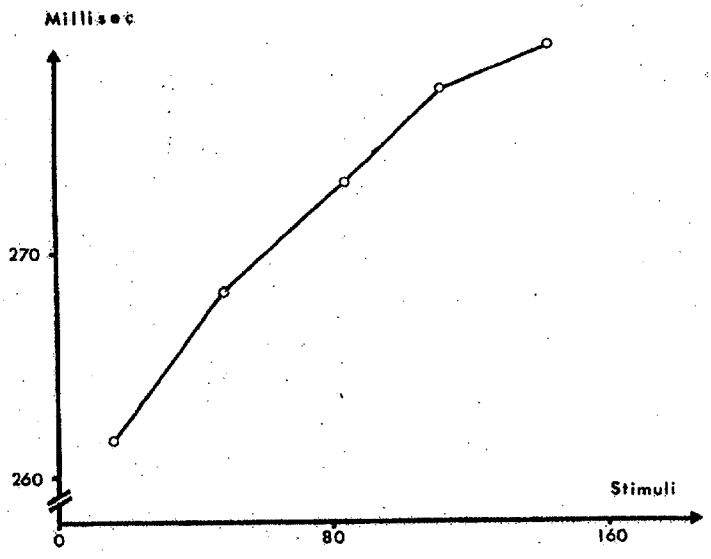

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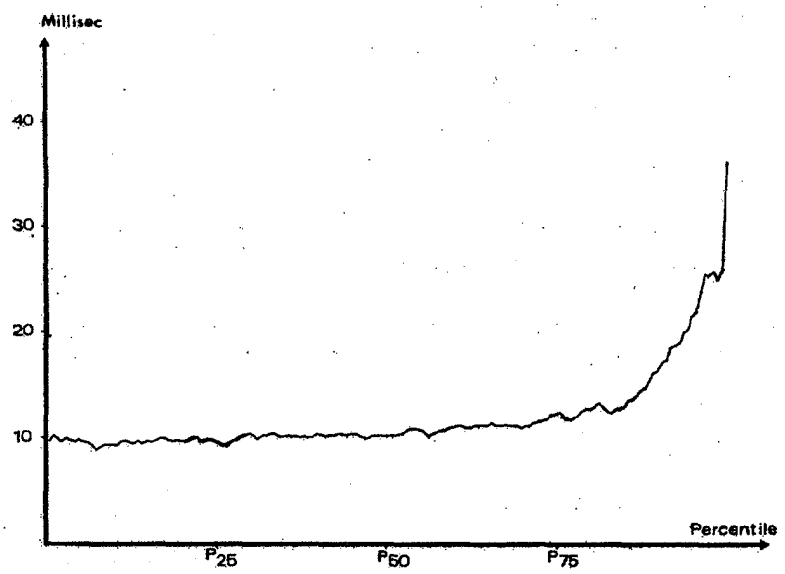

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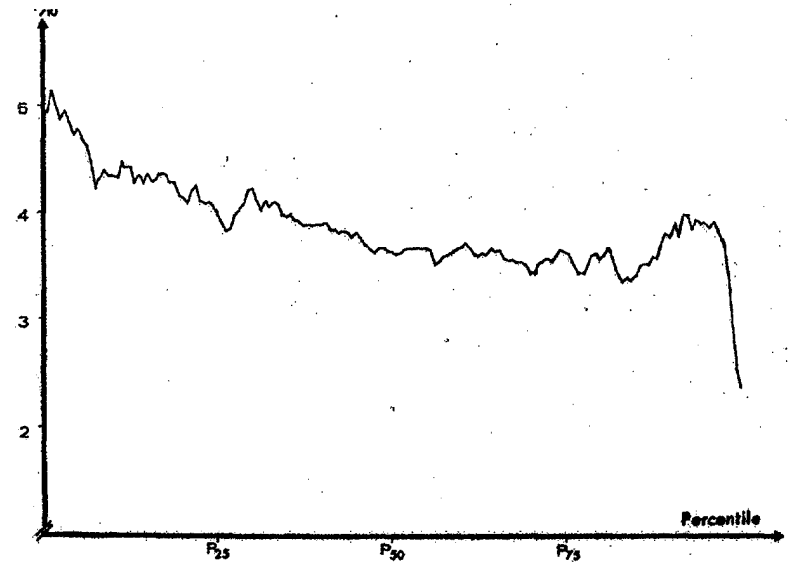

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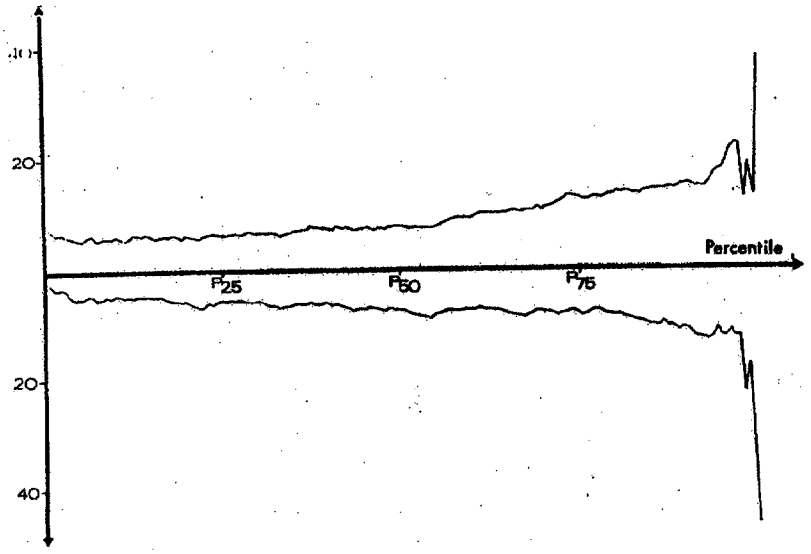

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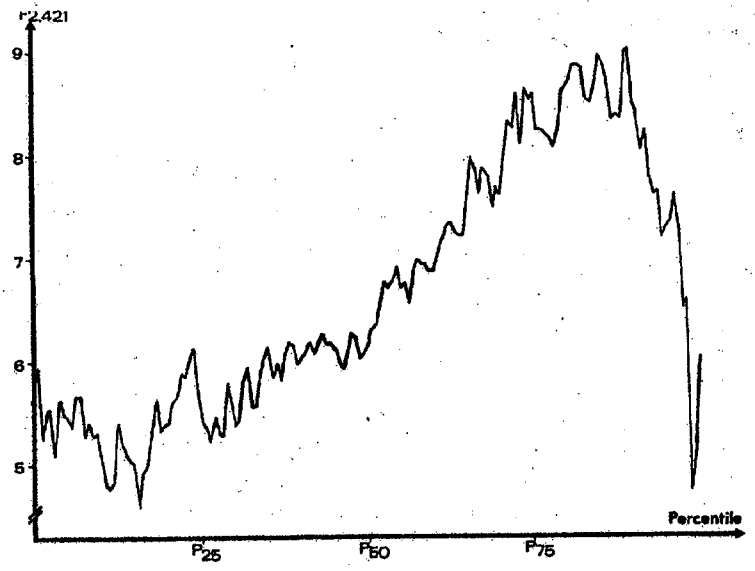

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