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Neuropsychological Effects of Industrial Toxins: A Review

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Quantitative assessment of nervous system function is essential in characterizing the nature and extent of impairment in individuals experiencing symptoms following workplace exposure. In recent years, the application of standardized neuropsychological tests to the evaluation of exposure to toxic industrial substances has significantly increased the understanding of the effects of these compounds. Within this review, the specific toxic neuropsychological effects of lead, carbon disulfide, trichloroethylene, perchloroethylene, mercury, styrene, and pesticides are discussed in detail. These discussions draw on our clinical experience with patients exposed to these substances as well as material from the medical literature. Factors affecting the utilization of these tests in occupational settings are also considered.

Key words: toxic substances, encephalopathies, neuropsychological assessments, behavioral effects of industrial toxins

INTRODUCTION

Chronic exposure to certain pollutants or byproducts of industry may result in behavioral changes in workers even before they are aware that the hazards exist or that they are being exposed. Ordinarily, descriptions of these symptoms are vague and case histories and anecdotal accounts in the literature seldom provide details concerning specific disturbances in cognitive function. There are reports of confusion, memory difficulty, apathy, or poor work performance in workers exposed to trichlorethylene, carbon disulfide, and toluene [Münchinger, 1963; Lindström, 1973]. Forgetfulness, headache, giddiness, and insomnia are often mentioned in reports of the effects of chronic poisoning by petroleum products [Takeuchi et al, 1975; Knave et al, 1977]. Axelson et al [1976] also reported a significantly high rate

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of nonspecific psychological complaints among painters, varnishers, and carpet layers exposed to solvents. Rarely cited are the results of neuropsychological tests. Although the literature contains much "soft" evidence of psychological disturbances, there exists a need for more quantitative documentation by use of standardized psychological tests. This communication reviews previous experiences with the use of standardized neuropsychological test instruments in subjects following exposure to various toxic substances known to affect the nervous system. Studies utilizing these tests would possibly lead to the development of toxin-specific protocols.

INORGANIC LEAD

The behavioral effects of inorganic lead have received increased attention during recent years, with particular attention to subclinical evidence seen with chronic low level exposure. Although results have been somewhat inconsistent, there is an increasing body of data pointing to characteristic features of lead-related behavior change.

In a group of secondary lead smelter workers, zinc protoporphyrin (ZPP), a biologic indicator of long-term exposure to lead, was found to correlate with measures of intellectual functioning (block design, digit symbol, embedded figure tasks), but not with a measure of coordination (Santa Ana: dominant or both hands) [Valciukas et al, 1978]. Performance on behavioral measures was age dependent with a fairly sharp decline occurring from age 50 in both exposed and control subjects. There was considerable individual variation in task performance at different levels of exposure. Hence, while group effects could be demonstrated, neither the ZPP level nor task performance could be used to predict lead toxicity in individual cases.

Hänninen et al, [1978] reported that lead workers whose blood lead levels (PbB) exceeded 70 μg/100 ml were significantly inferior on two tests of intelligence and several tasks of speed and control of psychomotor functions. She and her co-workers found impaired visual intelligence and visuo-motor functions in chronically exposed workers whose PbB never exceeded 70 μg/100 ml and who at the time of examination averaged only 32 ± 11 μg/100 ml.

Of all behavioral functions examined, visuo-motor dexterity (Santa Ana: right, left, and both hands) was most affected by lead uptake, as measured by actual, maximal, and time-weighted average blood lead (TWA PbB). Significant correlations were also found between TWA PbB and reduction in performance of visual tasks (block design and visual reproduction of Wechsler Memory Scale). Exposed group performance on other measures tended to be lower, but not significantly lower than the controls. Digit recall correlated only with actual PbB. The exposed group showed greater neuroticism on the Eysenck Personality Inventory, but this did not correlate with PbB level.

Unlike Valciukas and Hänninen, Repko et al [1975] were unable to demonstrate any effect on intellectual functioning as a consequence of exposure to inorganic lead, even though a large number of subjects (12%) had PbB values above 80 μg/100 ml. The tasks used, with the exception of digit span, were not the same as those used by Hänninen. Repko used measures from the multiple test performance battery of the Performance Research Laboratory, including signal detection, pattern discrimination, and mental arithmetic. Age and level of education were confounding variables and accounted for the major effect on performance. Visual acuity, immediate recall (digit span), and a subjective feelings checklist were also tested and found to be insensitive measures. However, increased tremor, slower and more variable eye-hand coordination, and higher mean hearing thresholds were found in the high-lead group. PbB was found to be not as sensitive to functional status in this study as was red cell aminolevulinic acid dehydratase (ALA-D). Repko found that controls were lacking in motivation to participate in the study and tended to perform both erratically and half-heartedly, thus providing an additional difficulty in interpretation of the results.

In a subsequent investigation, Repko et al [1978] extended work to include effects of inorganic lead on both behavior and neurological functioning. The aim of this effort was to develop a series of behavioral tests which could be used as a screening battery for effects of exposure to lead. The exposed subjects all had been exposed to lead for five years at the time of the study; none had mean PbB levels above 80 μg/100 ml. Auditory impairment reported in Repko's previous study, as well as a number of other studies [Balzano, 1952], was again documented in this investigation. Pure tone auditory thresholds were slightly higher for lead-exposed workers in both right and left ears across all frequencies except 800 HZ. Lead workers also showed more tone-decay at threshold and at 5 dB above threshold. Auditory threshold diminution was related to blood levels of free erythrocyte protoporphyrin (FEP). The hearing loss demonstrated in lead toxicity is most likely sensorineural, although a central hearing loss has not been ruled out.

The other deficit detected in this study involved psychomotor processes. Lead-exposed workers were significantly slower on a visual reaction time test using the right hand—a finding related to the decrease in motor nerve conduction velocity in the ulnar and median nerves also present in the lead group. No significant relationship was found, however, between reaction time and PbB.

Whereas functions associated with higher cognitive processes were not evaluated by Repko et al [1978], in a recent extensive study by Grandjean et al [1978], the full Wechsler Adult Intelligence Scale (WAIS) and several measures of short-term memory, learning, and attention were administered to exposed and control subjects. Significant differences were found between exposed and control groups in performance on several subtests of the WAIS (information, comprehension, similarities, vocabulary, digit symbol and picture arrangement). Also found were differences in digit learning, finger-tapping (using the nonpreferred hand), visual Gestalt reproduction, and performance on a graphic continuous performance test (CPT). Dose-response relationships were also noted between blood levels (PbB and ZPP) and several of these performance measures. Attempts were made to exclude individuals with preexisting neurological or psychological disease. Alcohol consumption history was comparable in the two groups. Information on education level was not presented in sufficient detail to assess the educational comparability of the test groups. Children are often found to be victims of toxicity and, therefore, have been subjects of epidemiologic evaluations. Byers and Lord [1943] found evidence of long-term effects of early lead poisoning in 20 children, primarily expressed in lowered intellectual functioning, great difficulty in learning in school, and behavioral problems, particularly hyperactivity and distractibility. Even though all the children's acute lead poisoning had occurred prior to school entrance, their exposure profoundly retarded school learning. There was overwhelming evidence of disturbances on perceptual motor tasks. Moreover, even early asymptomatic lead exposure in children has been demonstrated to have long-term consequences [de la Burdé and Choate, 1975]. Tested three to four years after exposure at ages seven or eight, many children were found to have neurological impairment. Psychological testing revealed that while many of the children were of normal intelligence, those performing in the borderline or mentally retarded range were more often than not in the exposed group. Significantly more lead-exposed children also performed in the suspect or borderline range on the Bender Gestalt, a measure of perceptual motor functioning, and on the auditory vocal association subtest of the Illinois Test of Psycholinguistic Abilities (ITPA).

Behavioral disturbances, such as reduced attention span, impulsive or uncontrolled behavior, and lack of self confidence expressed in fearfulness and need for attention and help, were noted eight times more frequently in lead-exposed than in control children. Hyperactivity in children exposed to lead even at subclinical levels has also been reported by others [Baloh et al, 1975; David et al, 1972; de la Burdé and Choate, 1975; Needleman, 1973], although this has been contradicted by Lansdown et al [1974], who could find no relationship between PbB level and intellectual functioning in children exposed to lead due to proximity to a smelter. In a study of 46 schoolchildren with PbB levels of 40–68 μg/100 ml and 78 controls (PbB: 40 μg/100 ml), Landrigan et al [1980] reported no difference in full-scale IQ, behavior, or hyperactivity. However, significant depression of age-adjusted performance IQ and slowing in a finger-wrist tapping test were found in the lead group.

Needleman et al [1979] found a variety of neuropsychological deficits in children who had been exposed to lead, cumulative exposure as evidenced by dentine lead levels in shed teeth of first and second graders. A comprehensive test battery, including measures of intelligence, academic achievement, auditory and language processing, visuomotor skills, motor coordination, and attention was administered to both high-lead and low-lead groups. The children with high lead levels performed significantly less well on the Wechsler Intelligence Scale for Children (Revised). Verbal functioning was particularly affected; the lowest subtest performed was on digit span. They also showed significant deficits in auditory processing, including tone discrimination, immediate verbal recall, and receptive language. Difficulty in sustained attention was demonstrated by a 12 second delay on tests of reaction time. Although no significant differences were found on an initial attention task with shorter delay (3 seconds), if readministered after 15 minutes of continuous testing, the high-lead group performed less well than the controls. The authors suggested that the high-lead group was more susceptible to fatigue and more distractible. No significant differences were found on other measures, notably those involving visuomotor skills and motor coordination. Teacher ratings of classroom behavior indicated that children with high levels of exposure were significantly more distractible, less persistent, and tended to daydream more than their counterparts with low exposure. Classroom behavior was found to be related to the level of lead exposure in a dose-response curve. None of the children with high lead levels did show effects on their intellectual functioning, verbal processing, attention, and classroom behavior—all of which might reasonably interfere with the ability to learn.

While maturity of the brain clearly diminishes susceptibility to toxic effects of lead, there are other differences between children and adults which may make detection of chronic effects of lead exposure more difficult in adults. Of interest here is the observation that a major long-term effect of lead exposure on children is impairment of learning. Occupational exposure, by its very nature, occurs in a situation where workers have already learned the task to be performed. Moreover, the longer they stay at the same job, the more practiced they become at it. Over-practiced skills are frequently the least vulnerable to any deteriorating central nervous system process except those of an acute or focal nature. Hence, for those who are chronically exposed because of long-term employment, it is only where new learning is required that impaired functioning becomes apparent. It is possible that tasks which are most like the ones routinely performed may not show impairment, while those demanding new learning may be more sensitive to subclinical effects. It seems likely that when deficits on tasks which require manual coordination and speed are evident in populations of workers who perform similar tasks daily, marked involvement of the nervous system is indicated.

Neuropsychological studies of lead-exposed patients in our Occupational Neurology Clinic do support this view. These patients show evidence of memory impairment, particularly in learning new material, and impairment on visuomotor and visual construction tasks. One of the subjects, a 31-year-old woman, was engaged in deleading a recently purchased older home, part-time, during the winter when there was poor ventilation in the house. After several months, she noted a feeling of irritability, headaches, cramps of the hands and calves, and frequent dropping of objects. She continued to feel weak, tired, and unusually depressed. A blood lead level obtained in the fall, nine months after she began the de-leading process, was 146 μg/100 ml. At that time, neurological examination revealed bilateral weakness of her wrist extensor muscles, with no other objective evidence of neurological dysfunction. Neuropsychological testing showed that she was above average intelligence but showed memory impairment, particularly in learning new material, and poor recall of visual design. Her processing of more complex visual material was impaired due to poor attention. Those subtests of the Wechsler Adult Intelligence Scale which were most affected by her lead exposure were the similarities digit span, digit symbol, and block design scales. Significant difficulty was demonstrated as well during the continuous performance test, which is a sensitive measure of impairment in concentration. She was hospitalized and received chelation therapy. Improvement in her performance I.Q. was noted on subsequent retesting seven months later. Use of a criterion measure, ie, an aspect of functioning which is generally impervious to toxins (vocabulary or verbal reasoning), has been of value in differentiating the effects of lead intoxication. A difference in score, derived by comparing performance on toxin-sensitive measures with the criterion measure, aided in the detection of psychological deficits due to toxic lead exposure in our patient.

CARBON DISULFIDE

Chronic exposure to carbon disulfide (CS_2) produces vascular changes, peripheral neuropathy, and symptoms of effects on the brain. In some patients a Parkinsonian syndrome is seen. Although dizziness and confusion are seen acutely, longer lasting and possibly more subtle behavioral changes may be overlooked. One of our patients, a 28-year-old man, working as an electrician in a rayon manufacturing facility developed symptoms which were difficult to characterize until neuropsychological tests were done. His history between July and September of 1976 included extensive exposure of up to seven days a week working in the solution room and around extruder machines. During a two-week period, he installed a carbon disulfide monitor. He was contaminated, in fact, and was doused by carbon disulfide leaking from pipes around which he worked. His shirt disintegrated where the liquid had soaked the cloth. While working in the viscose ripening room, he experienced eye irritation and nausea, resulting from CS_2 vapors. On several occasions, while working in the regeneration pit behind the extruder machines, he was exposed to pools of liquid CS_2. He frequently left work because of nausea, eye irritation, and difficulty in breathing. After two to three months, his family began to note changes in personality. He was irritable, forgetful, and appeared depressed. He had trouble remembering names of people he should have known, his mind wandered, and he had trouble following conversations. There was a loss of interest in his favorite recreational activities. While driving a car, he noted that his mind would wander. He had poor attention and concentration. At that time the patient had developed a tremor which interfered with his ability to hold his tools steady.

Psychometric studies disclosed a discrepancy between the verbal IQ of 96 and performance IQ of 88. Constructional deficits were found using tests of block design and simple pictorial puzzles. The Shipley-Hartford Conceptional Quotient was depressed (64), indicative of impaired intellectual efficiency and poor verbal abstract function. Ability for sustained attention was reduced on vigilance testing. Memory testing revealed difficulty in acquiring new information. There was poor performance on Smith's Symbol Digit Modalities test, reflecting inefficiency in perceptual motor speed, new learning, and sequential analysis.

The lower performance IQ and the difficulties in perceptual motor and sequential analysis functions on testing, combined with the poor attention span and memory were consistent with subacute encephalopathy due to toxic exposure to carbon disulfide. Very little improvement in performance was seen on reexamination two years after cessation of exposure. Although he was less irritable and his attention seemed slightly better, he was unable to work because of a general attitude of disorganization as well as his tremor.

Some of the most compelling evidence of psychological deficits related to industrial exposure to neurotoxins has been provided by Hänninan [1971] in her study of effects of CS_2 exposure in workers in the viscose rayon industry. She employed an abbreviated battery which included WAIS digit span, similarities, block design, picture completion, and digit symbol; Bourdon-Wiersma Vigilance Test, Santa Ana Dexterity Test, symmetry drawing, Benton Visual Retention Test, Rorschach and Mira Test. This work demonstrated a broad range of effects which could be differentiated in acute and latent poisoning. Three age-matched groups were studied: clinically poisoned with exposure to CS_2 from six months to 20 years (Manifest Group); workers continuously exposed for 5–20 years (Latent Group); and workers, half of whom were occasionally exposed, but neither intensely nor continuously (Control Group). Many areas of poor performance, rather than a single deficit in functioning, separated the groups. The poisoned workers were particularly disturbed in their psychomotor functioning, dexterity, and alertness. They also showed a decline in intellectual processes requiring visualization, were less spontaneous, and had retarded speech. Exposed (Latent Group) workers also showed motor disturbances and impaired visualization but were normal in their speech. Personality changes noted in the Manifest Group were not observed in the Latent Group, but there was evidence of diminished originality and spontaneity on the Rorschach Test among the latter workers. Overly methodical performances on some tasks could be interpreted as indications of depressive mood or efforts to compensate for perceived weaknesses.

Further inspection of the Hänninen data reveals that only three tasks reliably discriminated in gradients of performance among all three groups. These were the WAIS digit symbol task, a measure of psychomotor speed, coordination, and ability to learn number-symbol associations; the Santa Ana Dexterity Test (right and left hands); and a measure of psychomotor behavior of the Mira test. The Santa Ana Dexterity Test was the most sensitive in detecting differences among the three study groups. With the exception of the digit-symbol task, measures of intellectual functions were less consistent in showing differences between exposed (Latent) and controls than any other comparison. These differences occurred on abstract visual-spatial concepts (block design) and verbal memory (digit span). Thus, these findings suggest that decline in intellectual functions may be of value in differentiating workers with chronic latent exposure from control groups, whereas motor function, while mildly impaired in chronic exposure groups, is more severely affected in manifest poisoning. Impaired motor function was present in workers exposed to CS_2 in studies [Hänninen, 1974] where lowered speed on behavioral measures and results of electrodiagnostic peripheral nerve testing were indicated.

Tuttle et al [1976] were able to provide corroboration of Hänninen's work by employing the same tests to measure behavior (WAIS digit span, digit symbol, block design, and the Santa Ana Dexterity Test) in addition to their own instruments which included a "feeling tone" checklist, reaction time tests, a vigilance task (Neisser Letter Search) critical flicker/fusion frequency, and color vision test. Exposure was estimated by iodine azide test, an analysis of CS_2 metabolites excreted in the urine. As in the earlier Hänninen [1971] study, performance on digit symbol and the Santa Ana tests correlated well with extent of exposure. Dose-response relationships were also evident with reaction time and vigilance tasks and block design. However, it is clear that age was responsible for some of these associations. After controlling for age by statistical methods, there were fewer consistent relationships. Performance on reaction time, Santa Ana (right hand), and block design did correlate with results of clinical neurological and electrophysiologic parameters. The findings of Tuttle support the previous work of Hänninen in that similar deficits were seen. Differences in the magnitude of effect may have been due to differences in amount of exposure among the workers in the two study populations.

Most investigations of the effects of CS_2 have focused on visuomotor functions, attention, and intelligence, which are motor and congitive processes primarily dependent on the integrity of the central nervous system. Other behavioral disturbances, called pseudo-neurasthenic difficulties by Lilis [1974], have also been related to CS_2 exposure. These difficulties include changes in mood or personality, excessive irritability, increased physical complaints such as headache, dizziness, weakness, fatigue, and memory loss. In a study of 84 young workers with confirmed poisoning from relatively moderate durations of exposure (maximum of six years, $2/3 < 2$ years) to CS_2 concentrations often exceeding 60 ppm, Lilis found that these complaints preceded the onset of more obvious neurological involvement, ie, peripheral neuropathy. Frequently, depressive changes in the workers were seen. Similar complaints were encountered by Tuttle et al [1973] in workers exposed to concentrations varying from 4.3 to 129 ppm, and also in workers from their more extensive 1976 study. General fatigue, insomnia, parathesias, and headache were found by Seppäläinen [1974] to be prominent clinical complaints of chronically exposed workers in whom central and peripheral nervous system lesions were found.

In summary, carbon disulfide has been shown convincingly to cause impaired psychomotor function, especially affecting dexterity and speed. Tests shown to measure these changes reliably include the Santa Ana Dexterity Test and tests of simple reaction time. Higher cortical functions, especially visuomotor abilities and concentration, are also affected by CS_2 exposure and are best assessed by block design, digit symbol, and digit span subtests of the Wechsler Adult Intelligence Scale. Age standardization of scores is essential to the proper interpretation of measures. Subtle symptoms such as mood change, irritability, and increased systemic complaints may precede overt neurological illness due to carbon disulfide and should be assessed by use of standard interview questionnaires.

TRICHLORETHYLENE

The greatest implication for adverse response to exposure to trichlorethylene (TCE), especially at the work site, is that it predisposes an individual to an accident [Chalupa et al, 1960] by affecting coordination and attention. Stopps and McLaughlin [1967] studied a human volunteer who was exposed to 200, 300, and 550 ppm of TCE for two hours and 45 minutes. His only complaint was drowsiness. At 550 ppm there was a marked decrease in performance on the Necker Cube Test Tasks. Salvani et al [1971] found decrements in tachistoscopic perception, manual dexterity, complex reaction time, and memory (Wechsler Memory Scale) in volunteer subjects exposed to average vapor concentration of 110 ppm, which is quite close to the Threshold Limit Value (100 ppm) for TCE. Greatest deficits were seen in the most complex tasks. Decrements in coordination and attention (random number inspection task) were found in normal volunteers exposed to TCE vapor in varying concentrations for 1, 2, or 8 hours per day during a week's time [Stewart et al, 1974a]. Stewart et al [1974b] attempted to replicate Salvani's work and, in addition, used a condition of exposure to 50 ppm TCE vapor in an effort to examine the dose-response relationship. The Flanagan coordination test and digit inspection test, found previously to be sensitive to TCE, were added to Salvani's battery. Subject variability was found to account for most of the results obtained. Furthermore, they were unable to duplicate either Salvani's or their own previous results using these particular measures of behavior.

The behavioral aspects of TCE intoxication in workers have usually been overlooked. One of the subjects previously reported by us [Feldman et al, 1970] demonstrates complex behavioral changes associated with exposure to TCE. An owner of a carburetor cleaning plant, the patient had been acutely intoxicated with vapors of TCE. His recovery from confusion, headache, and dizziness was followed by evidence of peripheral neuropathy. His peripheral symptoms of numbness and muscle cramps persisted for almost two years after exposure. It was his change in personality (not described in our earlier report) that was hard to explain except as a correlate of his difficulty in solving sequential problems and poor memory affecting acquisition of new information. He eventually lost his previously successful business. Follow-up thirteen years after the exposure showed persistence in his difficulties in solving multiple step problems and even making business decisions. These deficits escaped formal neuropsychological testing techniques.

PERCHLOROETHYLENE (PCE)

In a study of dry cleaner workers Tuttle et al [1977], using the Santa Ana Dexterity Test, Wechsler digit span and digit symbol, the Neisser letter search, and simple and choice reaction time could not demonstrate deleterious behavioral effects of exposure to perchloroethylene (PCE). However, an increment in performance was found between morning and afternoon testing. Mean 8-hour TWA exposure was 18 ppm over a five-day testing period. Critical flicker/fusion was found to be affected in exposed workers, but this correlated with fatigue rather than PCE.

While Stewart et al [1977] found significant decrements in performance on the Flanagan coordination task in subjects exposed to 100 ppm PCE over a 5.5-hour day, this was not a consistent result and may have been due to variations in dose effect. On some days the significant decrement at the same exposure level was not found. No other behavioral measure was deleteriously affected by PCE, either at that exposure level or a lower one (25 ppm). Alcohol ingestion at 1.5 ml/kg had more deleterious effects on behavioral measures. Slowing occurred on the Michigan eye-hand coordination test, reduction in performance on the Flanagan Coordination Task, and number of errors and time on target on a rotary pursuit task. No interaction effect between PCE and alcohol could be demonstrated on behavioral measures even though alcohol did raise PCE blood level during low (25 ppm) exposure days. Effects of diazepam dosages of 6 mg and 10 mg, both alone and in combination with PCE, did not affect the coordination tasks but did increase time of target on the pursuit rotory tasks.

In all, while PCE at high levels of exposure may produce effects on coordination, these effects are erratic. Other behavioral effects have not been demonstrated.

MERCURY

Behavioral effects of occupational mercury exposure have been described for many years in numerous clinical reports of exposure to metallic mercury, inorganic mercury compounds, and organic mercurials. Recently, quantitative psychomotor testing of workers with chronic low-level exposure to inorganic mercury has expanded our knowledge of the behavioral effects of mercury exposure. For example, we examined a 29-year-old man who had been employed for eight years in a chloralkali plant. His job consisted of maintenance and operation of the electrolytic cells. Four years after beginning work in the plant, he began to notice increased nervousness and irritability. His nervousness continued for two years and he began to experience a tremor of the hands, bleeding gums, easy fatiguability, increased salivation, and appetite disturbances. He sustained an injury to his left Achilles tendon and was away from work for seven months, during which time most of his symptoms improved. Tremulousness, nervousness, shyness, and depression were his most prominent residual symptoms. The patient and his wife described him as outgoing, calm, and patient prior to his employment at the plant. He had been a military policeman in the Marines and did not experience emotional upsets during his tour of duty.

Urine mercury monitoring had been performed by his employer during his entire period of employment and revealed numerous readings over 500 μg/liter, the highest of which was 736 μg/liter in his fifth year of employment. A blood mercury level performed in his sixth year at the plant was 8.2 μg/liter.

Physical examination performed at the end of a seven-month "vacation" from work no longer showed evidence of tremor, but a mild loss of pin prick sensation on the dorsal aspect of his arms was still present. Lines of increased pigmentation at the gingival margins of several teeth persisted.

Neuropsychological testing showed normal levels of intellectual functioning (full scale IQ, 97). There was no significant discrepancy between verbal and performance IQ scores. However, he showed moderate defects in his ability to perform mental calculations and in his verbal and visual memory. Written spelling was particularly impaired (considering his level of education) in that he showed an inability to copy simple sentences. He showed difficulty in concentrating on various tasks and, as a result, his performance was erratic with incorrect answers to simple questions and correct answers to more difficult ones. He was emotionally labile in the test situation appearing extremely anxious and depressed. He displayed average performance on the Santa Ana Dexterity Test and the digit symbol subtest of the Wechsler Memory Scale. This patient's illness was manifest primarily in emotional disturbances which had secondary effects of performance on standardized tasks of psychological performance. Although he showed no particular deficits in memory, psychomotor performance, learning ability, and recall of current events, his most striking deficit was one of impaired concentration which resulted in erratic performance on various tests. These effects were still detected seven months after he was removed from mercury exposure.

The chemical form of mercury to which persons are exposed is a major determinant of the nature of central nervous system toxicity. Metallic mercury toxicity and, occasionally, inorganic mercury toxicity are associated with a set of nonspecific behavioral symptoms consisting of self consciousness, timidity, anxiety, inability to concentrate, and irritability [Browning, 1969]. More advanced cases may exhibit personality change and loss of memory. Organic mercurials, particularly alkyl mercury compounds, have a strong affinity for the central nervous system and excessive exposure is associated with impaired intellectual functioning ranging from impaired calculation ability to severe mental retardation [Kurland et al, 1960]. Depression, irritability, and impaired memory have also been reported in patients with overt intoxication from organic mercurial compounds [Gerstner and Huff, 1977].

Although these clinical reports have documented the occurrence of behavioral abnormalities following mercury exposure, quantitative dose-response relationships were not attempted. Recent work using standardized techniques of assessing psychomotor function have shown dose-dependent impairment in workers exposed to inorganic mercury [Miller et al, 1975]. Eye-hand coordination, as measured by a maze test, finger-tapping, and reaction time were impaired in workers with elevated mercury body burdens. No tests of higher intellectual function were performed. Of particular interest in that study and in subsequent work from the same group [Langolf et al, 1978] is the finding that quantitative analysis of surface electromyograms (EMG) demonstrates a mercury-related shift in the tremor spectrum which was reversible after the cessation of mercury exposure.

In summary, mercury compounds, particularly organic mercurials, affect the central nervous system, and toxic exposure is associated with behavioral changes. Standardized testing has shown that mercury impairs psychomotor function with deleterious effects seen on the Michigan maze test, standard reaction time measurements and surface electromyographic studies of tremor pattern.

STYRENE

Volunteer studies performed by Stewart et al [1968] showed that single brief exposures (up to seven hours) of up to 375 ppm styrene in air were associated with transient impairment in manual dexterity, as measured by the Crawford Collar and Pin Test, and incoordination, as measured by the Flanagan Coordination Test. Symptomsof lightheadedness and headache often accompanied an abnormal performance on a modified Romberg test. Lorimer et al [1976] found a significant prevalence of a feeling of lightheadedness, most predominantly in workers with high exposure duration of more than seven years. Formal behavioral testing was not performed. Convincing evidence that excessive styrene exposure has a deleterious effect on several parameters of behavioral function has developed from a series of studies at the Institute of Occupational Health in Finland. In their initial behavioral study, Lindström et al [1976] found impaired visuomotor speed, visual memory, vigilance, and psychomotor performance using a large battery of behavioral tests. No effect on memory or intelligence was seen. A second study [Härkönen, 1977] showed increased rates of fatigue and difficulty in concentration in groups exposed to styrene. No correlations were found in this study between urine mandelic acid levels and symptom rates. Symptoms did not correlate with performance on behavioral tests previously reported by Lindström et al [1976]. Härkönen stated that the failure to demonstrate a correlation between symptoms and urine mandelic acid level suggested that the urine assay may not have been an adequate exposure monitor when exposure levels fluctuate widely. The lack of correlation between symptoms and test performance may be due to the fact that the particular indices selected measure different aspects of styrene toxicity and, therefore, are not sensitive enough to reveal deficits in function. Most recently, this group [Härkönen et al, 1978] has found evidence of impairment in visuomotor accuracy measured by the Symmetry Drawing Test, in psychomotor performance (the Mira test), and in visuomotor accuracy and attention (the Bourdon-Wiersma Vigilance Test) among styrene-exposed workers. In addition, dose-response relationships were noted between urine mandelic acid excretion and performance on these tasks.

Generally, styrene exposure is associated with symptoms of lightheadedness which increase in frequency with increasing levels of styrene in air. Behavioral testing of chronically exposed workers shows impaired psychomotor performance, vigilance, speed, and visual memory. Other memory functions and global intelligence measures are generally unaffected. Tests which have been shown to be of value in evaluating styrene effects on behavioral parameters include the Bourdon-Wiersma Vigilance test, the Symmetry Drawing test, the Mira test, the Crawford Collar and Pin test, and the Flanagan Coordination test.

PESTICIDES

Organophosphorus (OP) exposure produces confusion in patients with acute poisoning. Metcalf and Holmes [1969] administered the Wechsler Adult Intelligence Scale, Benton Visual Retention, and a story-recall test to a group of workers involved in the manufacture of OP compounds. No difference between exposed and non-exposed groups was found in the prevalence of overt clinical neurological signs such as sensory or motor deficits. However, slowness of thinking, calculation, and memory deficit were noted. In addition, exposed men reported symptoms of fatigue, irritability, changes in libido, sleep habits, and memory far more frequently than non-exposed men. These occurred mostly in those workers with a history of frequent and/or intense exposure. While quantitative differences were not found on neuropsychological tests, qualitative measures based on the efficiency with which test material was handled by subjects did reveal differences. The exposed groups were shown to have poor memory and difficulty in maintaining alertness and appropriate focusing of attention. Moreover, they frequently utilized compensation techniques such as delay, inappropriate giving up, and slowing down. These maneuvers contrasted with controls whose errors were usually inaccurate answers or faulty information. In a study [Mick, 1974] designed as a follow up of the work of Metcalf and Holmes, measures of proprioception, memory, linguistic competency, anxiety, and depression (Taylor Manifest Anxiety Scale) failed to produce any significant evidence of impairment except in heightened anxiety. Since the measures used were different, and qualitative analysis which had provided the detection of differences was not utilized, the study provides no evidence with regard to the replicability of Metcalf and Holmes' methods. Effects of OP on vigilance and complex reaction time on the same subjects used in Mick's study were investigated by Rodnitsky [1974], who was unable to demonstrate any significant impairment in exposed subjects in these tasks. Jusic [1974] found improved functioning in visual memory and constructional praxis tests following OP exposure using a test-retest design which was attributable to practice effects.

In all, the neuropsychological effects of organophosphates have not been studied adequately. The qualitative methods of Metcalf and Holmes suggest a viable approach to detection of subclinical effects which deserve further investigation. Otherwise, the research on OP has been fraught with technical problems and designs which do not suit attempts at replication.

DISCUSSION

The most frequently reported behavioral effect of neurotoxins is a disturbance in psychomotor functioning. Ordinarily, this is characterized by a delay or slowness in response time, clumsy or awkward eye-hand coordination or dexterity, or a combination of these. Diminished attention or vigilance has also been found mainly during tasks requiring a motor response. An exception to this is the effect of CS_2 exposure on the Neisser Letter Search Vigilance Test, which is not primarily a motor task. A number search task was reported sensitive to TCE, but the authors were unable to replicate the results. Though this essentially motoric deficiency has been measured in a number of ways in investigations of behavioral effects of neurotoxins, the review of the literature suggests that when a behavioral disturbance is found, it is most likely to be one which has a major motor component regardless of the toxin studied. Moreover, a decrement in psychomotor functioning appears to be one of the few behavioral functions for which evidence of progressive impairment related to the degree of exposure can be demonstrated.

Aside from those of psychomotor functioning, the most frequently found effects of neurotoxins are nonspecific behavioral disturbances. These range from neurasthenic symptoms and mild depression to flagrant toxic psychosis. The latter is most characteristic of acute solvent poisoning, carbon disulfide, or tetraethyl lead. The repeated reference to neurasthenic symptoms in chronic low level exposure to neurotoxins predating onset of more frank clinical symptomatology deserves attention. The impression conveyed by prior work is not that such symptoms do not exist, but that efforts to measure them reliably have been difficult. Development of reliable and effective measures of these symptoms offers a promising avenue for investigation of early effects of toxins.

To be sure, other behavioral effects of neurotoxins have been reported. In some cases, these effects have been more purely on sensory functions such as auditory threshold or visual perception. In other cases, effects on higher cortical functioning have been reported. Most reports of effects of neurotoxins on intellectual functions have originated in Scandinavian countries, and efforts to replicate the results in U.S. workers have largely not been successful. This is particuarly true for chronic low levels of exposure.

A decline in intellectual functioning and particularly memory tends to be found, if at all, in cases of acute poisoning, except when solvents are the toxic agent. Effects of chronic CS_2 exposure on behavioral functions, particularly visual intelligence, in workers who appear relatively well have been reported [Hänninen, 1971]. However, these have not been found reliable [Tuttle et al, 1976] when age has been co-varied. Moreover, there is some evidence that a decline in higher cortical functions may be more readily observed with solvents rather than in chronic metal exposure such as with lead. This relationship appears to hold more strongly for adults than children. The disastrous effects of lead on mental development in children are well documented.

Factors Affecting Documentation of Effects on Behavior

The question arises as to whether the general failure to find reliably cerebral effects of neurotoxins in this country, except in cases of acute poisoning or solvent exposure, is an indication that such effects occur only erratically except in poisoning sufficient to induce acute encephalopathy or whether the attempts to measure effects have been inadequate. The evidence, usually on the basis of individual case reports, though certainly not conclusive, suggests that cerebral effects do occur and that they may be irreversible once poisoning, manifest by other clinical symptomatology, is present, even after appropriate treatment. Long term sequelae characterized by diminished intellectual functioning and memory following acute poisoning have been reported. Moreover, careful histories have revealed that complaints, particularly of diminished memory, frequently predate the onset of other symptoms, sometimes by years. This is so even when measures of exposure, eg, blood level, have been considered below hazardous standards. That effects from chronic low level exposure can at times be found in the research in other countries suggests some additional albeit not persuasive, support for the view, not only that cerebral effects do occur with low level chronic exposure, but also that the methods of measuring them may be inadequate. The major problem has been one of replicability. Frequently, studies of behavioral effects of neurotoxins by U.S. investigators have failed to utilize the same measures as those showing effects in other studies. This is due partly to lack of availability of the measures to be employed. Difficulty in detecting effects may be due to lack of sensitivity of instruments. When intelligence and memory tasks have been utilized, abbreviated versions of these have been given. While they may have value in discriminating effects when very low performance is anticipated, such tests are poor discriminators of subtle effects. In addition, no relatively stable measure of intelligence such as vocabulary has been given concomitantly so that comparison can be made of one function with another. In view of the failure of many studies to control for intelligence level and educational background, it is likely that failure to demonstrate effects may be related to inadequate control of confounding variables rather than to the true effects of exposure. A number of methodological inconsistencies in previous studies limit the ability to draw significant conclusions. These include failure to adequately control for age, interactions with other neurotoxins, especially alcohol and level of intelligence and educational background. Many studies have failed to provide adequate controls for these during data collection and have sought to control for them after the fact. If adequate matching of control and exposed populations is not performed in the design stage of the study, control by statistical manipulation may be difficult, if not impossible.

Behavioral effects of neurotoxins vary in clinical features depending upon the particular substance and intensity of exposure. Acute intoxication often produces symptoms such as dizziness, confusion, lethargy, and motor incoordination. Subacute and chronic exposure result in changes in those functions concerned with memory and problem solving ability. Low level exposure results in the accumulation of tissue concentrations of the toxic material. The central and peripheral nervous systems are particularly vulnerable to certain heavy metals, solvents, and organophosphates. While subclinical toxic peripheral neuropathy can be measured objectively by the technique of nerve conduction velocity, the neurobehavioral effects have been more difficult to document because of the possible subjective response to some of the instruments employed. Quantification is poor because of lack of standardization and nonspecificity of some of the tests. These factors are of serious concern when trying to screen populations at risk for the more subtle effects of neurotoxins, as well as documenting the extent of damage a victim may have suffered by a known intoxication.

There are seven categories of neurobehavioral disturbance which have been found in association with intoxicating levels of certain substances. These include memory; overall intelligence and problem solving; sustained attention; dexterity and eye-hand coordination; reaction time; psychomotor function; and tests of personality or mood. From the many studies considered in this report and our own experience, a battery of tests appear useful for detecting the behavioral effects of neurotoxins (Table I). The principal difficulty in evaluating behavioral effects is the relative lack of available standardized neuropsychological tests which can be administered to exposed workers in a practical period of time, and which can then be scored and interpreted with reliability, accuracy, and reproducibility. Any study of potential neuropsychological effects of neurotoxins must be done with correlative evidence of the exposure intensity utilizing tissue, and environmental concentrations of the suspected toxin must be strictly maintained.

TABLE I. Commonly Used Tests to Detect Behavioral Effects of Neurotoxins

1. Tests of Memory
   A. Wechsler memory scale
      Subtests: personal information, orientation, mental control, logical memory, digit span (forward and backward), visual memory, paired associate learning
2. Tests of Overall Intelligence
   A. Wechsler Adult Intelligence Scale (WAIS)
      Subtests: information, comprehension, arithmetic, similarities, digit span, vocabulary, digit-symbol, picture completion, block design, picture arrangement, object assembly
3. Tests of Sustained Attention
   A. Continuous Performance Test (COT)
   B. Bourdon-Wiersma Vigilance Test
   C. Neisser Letter Search
4. Tests of Dexterity and Eye-Hand Coordination
   A. Santa Ana Dexterity Test
   B. Flanagan Coordination Test
   C. Michigan Eye-Hand Coordination Test
   D. Finger-tapping Test
5. Test of Reaction Time
   A. Simple
   B. Choice
6. Tests of Psychomotor Function
   A. Mira Test
   B. Digit-symbol Substitution Task
7. Tests of Personality or Mood
   A. Eysenck Personality Inventory
   B. Rorschach Test
   C. Feeling-tone Checklist

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