Clinical Neurotoxicology: Detection of Neurobehavioral and Neurological Impairments Occurring in the Workplace and the Environment

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MANY INDUSTRIAL and agricultural chemicals have harmful effects on both the central and peripheral nervous system. The following discussion addresses the problems of measuring dysfunction in the nervous system following exposure to such neurotoxins. Hopefully continued efforts in this field will result in the ability to perform neuroepidemiologic studies not previously possible. The literature[1,2] is filled with reports of neurotoxic diseases in workers to which the reader is referred.

Behavioral Toxicology

Behavioral toxicology has been used to relate behavioral assessments of workers to chemical exposures that have occurred in the workplace. As summarized by Johnson and Anger,[3] behavioral toxicology is currently used as:

a. An indicator of functional impairment at exposure levels below those that produce overt tissue or organ damage.
b. A relatively simple, noninvasive means to monitor the effects of workers' exposure to toxic chemicals in health surveillance programs.
c. A complement to other methods (e.g., neurological) that provides functional correlates of clinical procedures and supplies toxicity information bearing on the central nervous system.
d. An indicator of impaired behavior that could compromise the safe performance of a job.

The potential usefulness of behavioral toxicology is realized, but which tests will detect subtle, sub-clinical neurotoxic effects remains an issue. Smith and Langolf[4] have noted the need for precise, ability-specific tests because gross performance measures may not pose a sufficiently difficult task to detect the impaired function. This concern arises because of a general belief that there are often "compensating shifts in the method and manner of performance under adverse conditions or states of impairment."[5] Thus, when asked to perform a complex task or test, subjects may have available a number of alternative processing strategies or resource-allocation plans. If one cognitive system is impaired, subjects may select a strategy that minimizes the load on that system, effectively hiding the impairment.

The cognitive tests used in clinical neurology are frequently too imprecise and unchallenging to be of use in a study of subclinical effects.[6] It is likely that such gross performance measures involve the functioning of several "elementary components." There appears to be a trade-off using precise, specific measures of performance and using gross screening tests. A specific test is more likely to detect an impairment, but because of its specificity the chance of missing an impairment is greater. Performance on a gross test, on the other hand, may be influenced by the functioning of many elementary components but may be so susceptible to compensatory shifts in function that impairment of one of these elementary components is missed.

There exist other important limitations in the standardization of the techniques in behavioral toxicology. Test administration and scoring is often variable and as a result, the reproducibility of these instruments may be poor. Furthermore, various extraneous factors (potential confounding factors) may influence test per-

formance in a way that influences the attribution of the effects of exposure. Research in neurotoxicology has not developed sufficiently to integrate performance on specific tasks with specific neuropathological processes or disease conditions.

The functional domains which have been represented in varying degrees in neuropsychological test batteries given to workers to assess the effects of occupational toxins include motor speed, motor steadiness, attention/response speed, perceptual motor speed, manual dexterity, visual perception/memory, auditory memory, attention/vigilance, and verbal abilities. In May 1983, at the World Health Organization (WHO) International Meeting on Prevention of Neurotoxic Illness in a Working Population, a report was presented on psychologic test methods. The specific recommended tests for each functional domain are summarized in Table 1.

Changes in mood, emotional reactions, and personality are common features after toxic exposure. The assessment of these effects is difficult mainly because of the lack of suitable quantitative methods. Another problem is the difficulty in distinguishing primary toxic effects from more secondary reactions to the cognitive impairments or to anxiety about being exposed. Nevertheless, a comprehensive picture of the behavioral consequences of toxic exposures cannot be obtained without considering this category of effects.[3]

Symptom questionnaires yield information about how the subjects feel and their complaints. They have usually shown higher prevalences among exposed than among nonexposed subjects. Some of these group differences may be explained by the fact that the exposed subjects and the comparison group usually have different attitudes toward the symptom survey. Gradients of symptom frequency and increasing levels of exposure have been often inconsistent. The contents of items included in previous questionnaires has been reviewed.[3] Items dealing with fatigue and forgetfullness have proven to be most pertinent to excessive exposure, and in some groups, items dealing with the neurological symptoms.

Computer-administered tests for evaluating neurobehavioral functions in workers promise additional application in neurobehavioral assessment. The primary advantages of computer-administered tests are: standardization of test administration, objectivity in scoring, ease of data handling, greater flexibility in stimulus presentation and data acquisition, and avoidance of subjective factors in test administration time can be extremely accurate. A large quantity of information can

Table 1.—Proposed Psychological Test Methods*

Functional Domain	Screening Battery Minimum Program	Additional and Alternative Methods for a Standard Battery	Tests for In-Depth Studies or Tests to be Developed Further
Motor speed	Finger Tapping		Two-plate tapping
Motor steadiness	Flanagan Coordination or Mira	Aiming Tremometer	Body steadiness
Reaction time		SRT (60–100 signals) CRT	Series of RT-tasks with increasing complexity
Perceptual-motor speed	Digit Symbol, WAIS	Bourdon-Wiersma Neisser Identical Numbers	Combinations of different perceptual-motor speed test
Motor coordination	Santa Ana or some other dexterity test	Michigan Eye-Hand Coordination Purdue Pegbord	Other psychomotor tests
Visual cognitive functions	Visual Retention, WMS	Block Design, WAIS Embedded Figures Benton Visual Retention Symmetric Drawing	Picture completion, WAIS Object assembly (WAIS) Figure classification Memory-for-Design Test
Verbal abilities	Digit Span, WAIS, WMS Logical Memory, WMS Similarities, WAIS	Associative Learning, WMS Stroop Color Naming Test	Various memory span tests Memory tests with delayed recall Tests for auditory and semantic processing Verbal comprehension tests
Attention/vigilance		PASAT (Paced Auditory Serial Attention Test) Continuous Performance Test	Audiovisual Vigilance Test Other tests for attention and vigilance
Moods, emotions	POMS (Profile of Mood States)	Taylor Manifest Anxiety Scale EPI (Eysenck Personality Inventory)	Rorschach

* Presented at WHO International Meeting on the Prevention of Neurotoxic Illness in Working Population, meeting at NIOSH, Cincinati, Ohio, May, 1983.

be collected and stored for later (even unanticipated) analysis. Complex visual images can be presented for very short periods of time and in rapid sequences. Variations of tests and test items can be generated automatically. Tests can be scored and immediate feedback of results to those being tested may improve their motivation. Furthermore, the computer-administered format can change the nature of the test session from a potentially threatening and tedious situation to one with a challenging "game" quality. Obviously, it is premature to know whether the worker will appreciate the "game" quality or rather be insecure with the use of a computer-administered test. Problems may also arise with comprehension of instructions, measurement of verbal abilities and lack of adequate feedback to insure maximal performance.

Micro-processor band test batteries promise to revolutionize neurobehavioral assessment during the next few years and rapidly supplant many traditional tests. Micro-processor testing system should be available for general use for behavioral and electrophysiologic testing within 2 to 5 yr.

Tremometry

An increased tremor intensity may represent an early adverse effect of excessive exposure to some neurotoxic industrial chemicals (e.g., metallic mercury, lead, maganese, dichlorodiphenyl trichloroethane, lindane, lithium, methyl bromide).

Clinical examination of workers is not sensitive enough for detecting a slight change in tremor frequency distribution and amplitude. This was demonstrated by Miller[7] who performed a power spectral analysis of the forearm tremor in 77 workers exposed to metallic mercury vapor. In 27 workers the average tremor frequency was increased, although their clinical neurological examinations were normal. Also, quantifying hand tremor measurements is more reliable, sensitive, and better suited to quantitative statistical analysis than standard neurological tests. Tremor can be quantified by an integrator counter, which provides numerical scores proportional to the duration, amplitude, and frequency of the tremor, and by whole tremometer tests.[8] This tremor is conveniently recorded by a mechanical device measuring either displacement, velocity or acceleration. The tremor signals can then be subjected to Fourier Transformation to obtain a spectral analysis.

In another study by Wood et al.,[9] subjects were instructed to maintain a force on a finger-trough attached to a strain gauge, between a lower and an upper limit as signalled by two lights. The trials lasted 20 or 40 sec, with the arm either supported or unsupported. Frequency characteristics were described with power spectral analysis and the results expressed in arbitrary units of power spectral density in terms of frequency.

More recently, Schuckmann,[10] in his study of workers exposed to inorganic mercury in chloralkali plants, developed the following procedure. Subjects were seated with forearm fully supported and the hand freely movable from the carpal joint. The middle finger touched the sensor point of a piezo-electric receiver. The voltage changes induced by the tremor were recorded and a power spectrum obtained with the aid of Fourier analysis. The test lasted for two 20-sec periods and was repeated several times.

Chaffin and Langolf have published many studies; the first method[11] had the subject seated with his dominant arm supported by an elbow rest which allowed a 90° elbow angle with the forearm unsupported. A padded wrist cuff was strapped around the wrist to which both a force sensing tranducer and a 6.8 kg load were attached. The subject was instructed to pick up the load by flexing his arm to a 90° elbow angle and hold it. Then, by performing a power spectral analysis on the forearm tremor for the first 15 sec of the test, it was possible to quantify tremor frequency, distribution and amplitude.

In subsequent studies,[12,13] tremor was also recorded under very light muscular loading with the forearm supporting a light-weight pointer (285 g). The subject was asked to hold it as steadily as possible in an illuminated target zone. Recorded tremor signals were then analyzed to produce power spectra as described above.

Fawer's[14] study of 51 workers exposed to metallic mercury showed a good relationship between tremor measurement and indices of exposure. The subject was seated with an elbow rest which allowed a 90° elbow angle with the forearm and hand unsupported. A first measurement was carried out at rest for a period of 80 sec. A second measurement was then performed under load (1250 g) attached to the hand for a period of 80 sec, starting 5 sec after attachment of the load to the wrist. He recorded hand tremor by means of an accelerometer attached to the dorsal surface of the hand. Analysis of the records both included the determination of the highest peak frequency (frequency corresponding to the highest acceleration) and, as far as possible, the whole spectrum.

Each method was described to illustrate the different approaches resulting in the inability to make comparisons. Only Fawer[14] performed analysis of the whole spectrum; other investigators used only peak frequency thereby weakening the power of the spectrum analysis. For low exposure to metallic mercury, quantifying tremor is a more discriminatory test than writing.[14] As an objective screening test for early nervous system dysfunction tremometry has good potential but without a standardized approach differences in techniques may be the only comparison which will be made.

Evoked Potentials

Advances in electrophysiological procedures combined with micro-computers have stimulated the widespread use of sensory evoked potentials (EP) as an adjunct to the neurological exam. When properly performed and interpreted, EPs can provide an objective and reliable index of the functional integrity of sensory pathways from periphery to cortex.[15] EPs have proven particularly valuable in detecting clinically silent dysfunctions and in monitoring difficult patient populations.

Standard neurophysiological procedures for the detection of toxic neuropathies include measurement of

sensory and motor conduction velocities in peripheral nerves and electromyography (EMG). Slowing of peripheral nerve conduction has been correlated with a number of toxic axonopathies (e.g., n-hexane, acrylamide, etc.); however, the onset of change usually follows overt clinical signs and the computed velocity may be normal even when there is distal pathology in a significant portion of the axons. Similarly, EMG is principally sensitive to denervation of muscle fiber groups, a condition which typically signifies a state of advanced degeneration. Although the sensitivity of peripheral electrophysiological procedures can be enhanced by the use of stimulus trains,[16] or by the analysis of the distribution of conduction velocities,[17] these measures remain relatively insensitive to the early stages of toxic distal axonopathies.

EP's recorded from the scalp and spinal cord are manifestations of activity in multisynaptic pathway and can therefore be used as indices of the structural integrity of the distal extreme of the responding axons, as well as the neuro-chemical processes at the synapse. Recent studies in primates with acrylamide induced axonopathies suggest that changes in the timing and waveshape of short latency EP components antedate abnormalities of peripheral nerve conduction and behavioral signs of intoxication.[18] Hence, in many circumstances EP's may provide a more sensitive measure of neurotoxicity than peripheral tests. Furthermore, EP's afford a means of examining several modalities which may be differentially vulnerable to a given neurotoxin. Finally, EP's are the only noninvasive electrophysiological measure for these toxins that primarily affect central nervous system (CNS) fibers. The continued and expanded use of EP's as a noninvasive, objective measure of CNS function in man and experimental animals is virtually a certainty. The principal strengths of EP's as an index of neurotoxicity in human populations appears to be the sensitivity of this measure, the availability of reliable population norms, the ability to target vulnerable sites, and the ability to compare multimodalities.

Nerve Conduction Studies

As mentioned previously, measurement of sensory and motor conduction velocities in peripheral nerve are standard neurophysiological procedures used for detection of toxic neuropathies. Slowing of peripheral nerve conduction has been correlated with a number of toxic axonopathies; however, the onset of change usually follows overt clinical signs and the computed velocity many be normal even when there is distal pathology in significant portion of the axons. Sensitivity as a screening tool is problematic because more than 50% of nerve fibers must be blocked or lost before the amplitude of evoked action potential is outside normal limits.

The best electrophysiological test of peripheral nerve function is the analysis of the response to pairs of stimuli. This test is a more sensitive measure of axonal conduction deficit than is the single action potential, and is used in standard clinical technique. The use of stimulus pairs to detect neuropathies rests upon the requirement that detectable neurotoxic impairments are additive to the effects that occur in the relative refractory period (i.e., increased threshold, decreased height, decreased conduction velocity, and decreased safety factor). Since many neurotoxic substances decrease conduction velocity, it is reasonable to assume that they can be detected by this method. Most neurotoxic substances impair conduction by one of the above mechanisms. While not as sensitive a measure as a train of stimuli at high frequency,[15] the paired stimulus technique has the advantage that 50% of the effect measurable in the train is observed in the second response, i.e., a pair and sensitivity can be increased by decreasing the interstimulus interval. The method has been demonstrated to be sensitive in a number of different neuropathies including both segmental demyelination and axonal degeneration.[19,20]

An alternative suggestion is to use more refined electrodiagnostic techniques as a second level examination when searching for neurotoxic effects on the peripheral nervous system. For example, individuals with decreased perception of vibration could be studied further by recording sensory action potentials evoked by a probe designed to stimulate Pacinian corpuscles in man.[21]

Quantitative Sensory Testing

Sensory signs and symptoms are sometimes the only manifestation of early stages of nervous system intoxication. Due to the limitations in the standard neurologic examination and nerve conduction studies, especially when screening for early evidence of dysfunction in the peripheral nervous system, efforts are being directed to develop portable instruments for quantitative sensory testing. These instruments are precisely defined stimuli and sensitive testing and scoring to assess sensation. They can be automated to obtain optimum efficiency and eliminate both testing and observer variability thus eliciting responses which are both quantifiable and reproducible. Also, by using forced-choice testing, response bias can be greatly reduced so that inter- and intrasession variability is lower. A tracking method for stimulus presentation is sensitive and more efficient.

Most portable devices presently used to assess vibratory sensitivity are subject to damping an undesirable feature.[22] The most recent portable device to assess tactile and vibration thresholds, the Optacon Tactile Tester, is also subject to damping, but still has been used successfully in screening for toxic neuropathies.[23,24] Several laboratories are designing new instruments which will eliminate damping. Given that large-diameter axons carrying vibration sense are commonly affected by neurotoxins, the need for a portable device to screen workers is evident. These instruments detect and quantify sensory abnormalities, and when applied serially, worsening or improvement of sensation can be measured.

Tests of thermal discrimination provide evidence of involvement of a population of axons which now are not adequately evaluated by clinical neurophysiological

techniques. A portable quantitative thermal tester (Bailey Instruments, NJ) has recently been developed for research in diabetic neuropathy. It employs a thermoelectric cooling and heating unit with the ability to change temperature at a rate of 2/sec over a range of 40°C. Using "a two-alternate forced-choice method," most normal individuals can detect less than 1° difference between two test plates. Quantitative evaluation at this level of discrimination may identify involvement of smaller afferent axons in toxic neuropathies previously thought to only involve the larger afferent axons.

Measurement of Outcomes Secondary to Stress

In the workplace, exposure to neurotoxins frequently produces increased stress as a secondary effect which clearly may alter performance. Stress as defined below is the focus of considerable research which continues to have difficulty finding objective end points.

Selye[25] defined stress as a generalized pathological response to specific noxious stimuli. His concept referred to extreme or prolonged alteration either of the internal or external environment, which necessitated adaptation to restore homeostasis; the response involves either psychological or physiological changes which in time become pathological.

The study of psychological hazards in the workplace, i.e., "work stress," has been difficult to define with results being subject to multiple etiological interpretations. Disease outcomes are usually more strongly associated subjective perceptions and evaluations than actual work conditions. Finding new psychosocial predictors of disease does not necessarily further our understanding of the impact of psychological work hazards or what work conditions might need to be altered to prevent disease. Basic needs include the validation of measurements of stress and standardization of diagnostic instruments. These steps are essential before beginning the formidable task of identifying aspects of the psychological work environment which have disease consequence. One area that has demonstrated initial success in the study of psychosocial problems associated with the workplace is that of rotating shift work schedules that disrupt sleep.[26]

Within the past 50 yr round-the-clock operations in many industrial plants and emergency services has exposed 27% of male workers and 16% of female workers to major changes in the day-night shift schedules. Many work shifts rotate workers between night, evening, and daytime duties.

Numerous psychosocial problems have been associated with rotating shift work schedules. Over 80% of shift workers have serious sleep disruption (e.g., insomnia at home and sleepiness at work), and there is evidence of increased levels of cardiovascular risk factors and gastrointestinal disorders among shift workers. When schedules were introduced which took into account properties of the human circadian system, i.e., a phase delay once every 21 days, subjective estimates of work schedule satisfaction and health improved, personnel turnover decreased, and worker productivity increased.[27]

Most workers on phase advancing schedules may be in a state of continual forced internal desynchronization between the pacemakers of their circadian systems. The consequences of such disruption in temporal organization are just beginning to be understood. Biologic problems underlying shift work are further discussed by Moore-Ede et al.[28] It may be that the application of circadian principles to the design of schedules can maintain the temporal integrity of the circadian system and minimize for the shift worker any detrimental consequences of circadian disruption. Further studies are needed to examine the health consequences of shift work, but alternative solutions must also be explored since a phase delay every 21 days may not be suitable for all work situations requiring continuous staffing for 24 hr/day.

In summary, this article discusses problems and areas of current research as related to methodology in clinical neurotoxicology. It is clear that in all the areas covered, i.e., behavioral toxicology, tremometry, evoked potentials, nerve conduction studies, quantitative sensory testing, and measurement of outcomes secondary to stress, that a need exists for standardization and validation of the methods. This is a rapidly expanding field with many new tests in which caution must prevail to guarantee accurate interpretation of the results. Neuroepidemiologic studies of exposed populations using these tests should be possible in the near future.

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Cardiovascular Disease and Work Place Exposures

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THE CONCERN FOR A contribution to the development of heart disease from occupational exposure evolves from two considerations. (1) Although more is known about the risk factors of atherosclerotic heart disease than any other major condition, it has been estimated that currently known risk factors account for only 50% of the disease.[1] (2) The magnitude of the problem of atherosclerotic heart disease means that even if occupational factors are important in only a small proportion of the individuals developing disease, that a reduction in such factors may have important public health benefits. Preventive health measures that do not involve individual changes in life style are sometimes easier to implement. Despite recent declines in mortality from heart disease, approximately 1.2 million individuals have heart attacks each year, with over 600,000 deaths.[2] This computes to more one death every minute.

Neither of these considerations is specific to occupational factors, and in fact, has been used by investigators in other disciplines to justify research in their area (e.g., social risk factors). Such varied approaches are appropriate considering the known multifactorial etiology of heart disease. It is important that occupational investigators also devote sufficient resources to explore the primary cause of mortality in the United States.

The substances listed in Table 1 have been suggested to be associated with heart disease. The number of question marks in the table, especially for chronic effects, indicates the weakness in much of the supporting data. Although exposure to many of the factors in Table 1 is limited to well-defined occupational cohorts, other exposures, e.g., carbon monoxide or soft water with its excesses and deficiencies of certain trace elements, are important to a much larger population. The inclusion of work-related stress as a factor broadens the scope to include the majority of the adult population.

The difficulties in recognizing an increase in heart disease from occupational exposure include: