PART VII. TOXICOLOGY AND PHYSIOLOGY

EEG, PSYCHOLOGICAL, AND NEUROLOGICAL ALTERATIONS IN HUMANS WITH ORGANOPHOSPHORUS EXPOSURE*

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In the early 1950's, the University of Colorado Medical Center conducted a multidisciplinary investigation of industrial and agricultural workers acutely exposed to a variety of pesticides. The focus of this program was a special project involving the intensive study of workers engaged in the manufacture of several organophosphorus (OP) anticholinesterase compounds. Because of the acute confusional states induced by OP exposure and because of the need for more information regarding the central effects of OP exposure in humans, an effort was made to examine certain psychological, neurological, and clinical-neurophysiological variables; additionally, a number of biochemical parameters were investigated. Since January, 1965, a group of men from this same industrial population has been studied; many of the current subjects have been continuously employed in the same capacity since 1950. This report is concerned primarily with some of the psychological, neurological, and clinical-neurophysiological results of these studies.

In the 1952 program, psychological testing involved a large battery of measures designed to search for classic evidences of brain damage. Data analysis revealed no formal evidences of organic brain damage in psychological test terms. Testing done within 72 hours of exposure almost always showed erratic and slowed functioning, interpreted as indicating the presence of clinical delirium for many individuals within three days of a symptomatic exposure.

The one differentiating test in the original study was the Rotary-Pursuit task, a test of hand-eye coordination. Recently exposed men had worse performance than controls, but we have since found that this type of test is unreliable because of technical limitations.

Neurological examinations revealed multiple minor signs such as generalized weakness and confusion shortly after exposure; hard neurological signs were absent after treatment and clinical recovery. In the 1952 study, electroencephalograms were done as close to time of exposure as possible and, in many cases, repeated after treatment and recovery. Typical slow-wave bursts after activation by overbreathing were observed if EEGs were done soon after untreated exposure (FIGURE 1). These findings were similar to those reported by Grob (1953). At this time, it was believed that adequate treatment normalized the EEG. These old EEGs have been reevaluated in light of findings from our current investigations and modern knowledge of the neurophysiology of drowsiness and sleep. Upon reevaluation, we find an increase in medium-voltage, irregular theta activity, occurring in bursts of one to five seconds' duration, most often seen during light drowsiness. Special characteristics of the drowsy EEG—there is a normal increase in slow activity—made it easy to overlook this change.

In the 1952 study, psychiatric interviews were done on 78 men: 56 with histories

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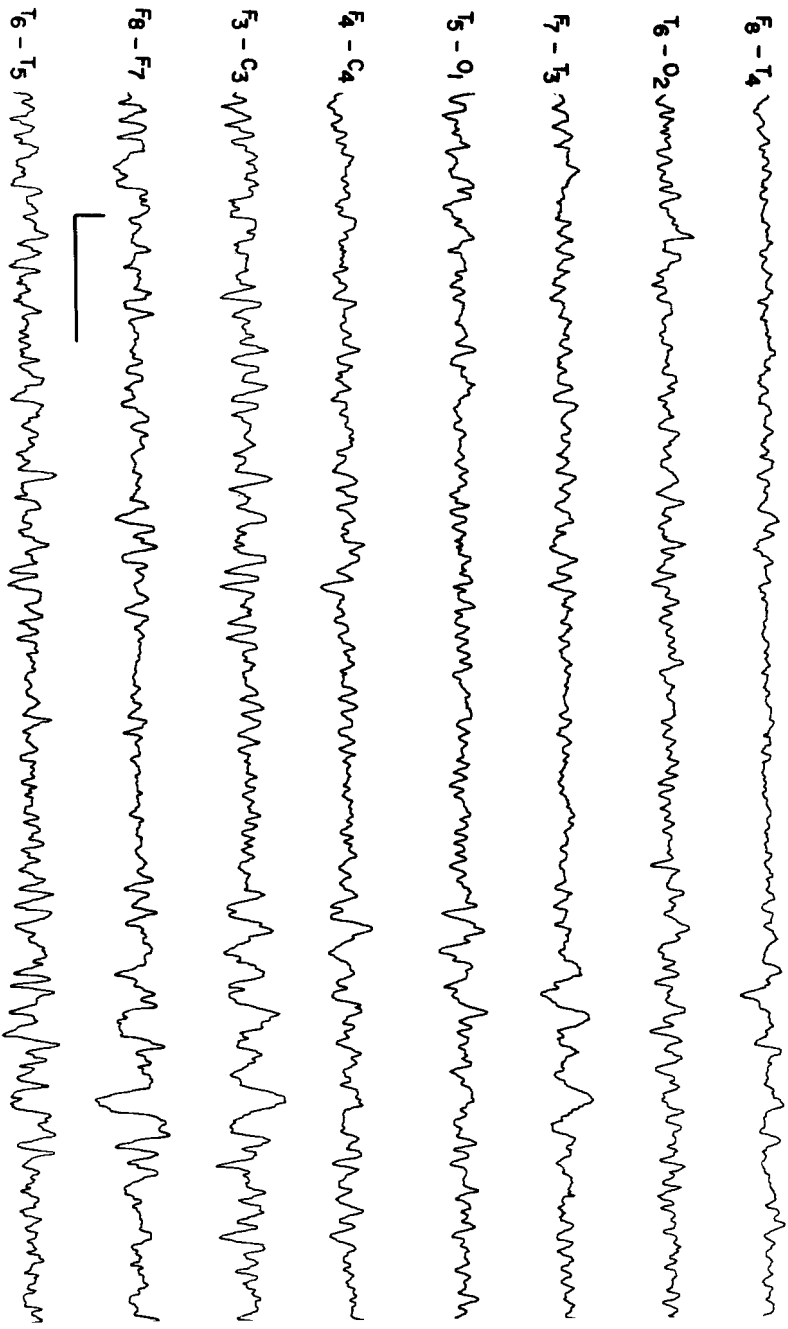

FIGURE 1. Slow Bursts seen with acute OP exposure.

TABLE 1

COMPARISON OF CONTROL AND EXPOSURE GROUPS* FROM RMA SYMPTOMS REPORTED ON PSYCHIATRIC INTERVIEWS

	CONTROL GROUP		EXPOSURE GROUP	
	Number Reporting Symptom (N = 22)		Number Reporting Symptom (N = 56)	
Irritable and impatient	11	50%	35	60%
Forgetfulness	5	20%	29	53%
General fatigue	1	5%	19	35%
Change in sexual desire – decrease	6	25%	14	23%
Increased dreaming	4	18%	10	18%
Trouble sleeping	2	10%	5	10%
Difficulty in thinking tasks	1	5%	6	12%
Lethargy, "Don't give a damn"	0	0	5	10%
Change in sexual desire – increase	0	0	4	7%
GI distress	7	30%	11	21%
Visual difficulty	0	0	14	30%
Nervousness				
Headaches	2	10%	7	14%
Muscular aches and pains	0	0	6	12%
Frequent colds	1	5%		
Increased perspiration	0	0	2	4%

* Average: 38.3 years; average time of employment: 77.68 months or 6.47 years.

of exposure and 22 controls. Significant chronic complaints were forgetfulness, difficulty in thinking, visual difficulty, and persistent muscular aches and pains (see TABLE 1). Drowsiness, fatigability, and loss of interest in work were complained of by 45 per cent of the exposed group and only 5 per cent of the control group. There was a less outstanding increase in reports of irritability in the exposed group. There were no significant differences for change in sexual desire, insomnia, headaches, or frequency of somatic disease, including upper respiratory infections.

The current study was designed to include psychological testing, interviews by a psychiatric social worker, electroencephalograms, visual and auditory evoked responses, neurological examinations, physical examinations, and a special all-night sleep study.

The relative lack of differentiating measures from previous psychological testing led to what has been a fruitful and revealing methodology focused on cognition. These measures evaluate the efficiency with which psychological test material is handled and the characteristic ways in which individuals adapt to such minimal functional deficits as poor memory. Although classic psychological signs of organic brain damage are searched for in our subjects, it is more likely that major interferences with functioning are minimal, may not depend on cortical processes alone, and are compensated for in a variety of ways. This scoring method emphasizes and considers in detail the adaptive and compensatory techniques used to some extent by most people in handling intellectual and performance problems. It is based on the clinical observation that individuals with minimal brain dysfunction develop characteristic ways of problem-solving and demonstrate thought-deficits that are unlikely to be detected by standard methods. These deviations may in general be classified as ways of avoiding problem-solving and delaying in order to gain thinking time, idiosyncratic and often oversimplified perceptual functioning, loss of ability to appreciate complex abstract relationships, and memory disturbances, which are masked by such adaptive "tricks"

as deliberately slowed responses and mnemonic aids. Eight adaptive mechanisms or categories of answers (see TABLE 2) were standardized on a population of 70 men varying in degree of exposure. This technique, called the Behavioral Classification System (BCS) provides a quantitative approach to an ordinarily subjective and unreliable evaluation.

The psychological test battery consists of the Wechsler Adult Intelligence Scale (WAIS), Benton Visual Retention Test, and a Story Recall Task.

The WAIS is analyzed in accord with formal published standards and also analyzed for cognitive and adaptive mode in accord with the previously noted BCS. The Story Recall Test is a specific memory task administered after the WAIS. Common adaptive compensations for memory disturbance, such as fabrication, are revealed here. The three forms of the Benton Visual Retention Test are administered. The task involves the drawing from memory of progressively complex geometric designs to test hand-eye coordination, perceptual accuracy, and memory. Perceptual distortions and memory disturbances are revealed here. When used as a cognitive measure, the interplay of immediate re-

TABLE 2

BEHAVIORAL CLASSIFICATION SYSTEM (BCS)

Categories for Information, Comprehension, Vocabulary and Similarities Subtests	
I. Delay:	
(a.) nonverbal delay	(c.) echo
(b.) verbal delay	(d.) subject-examiner interaction
II. Uncertainty:	
(a.) implicit and explicit – self directed	
(b.) examiner directed	
III. Response failure	
Categories for Digit Span Subtest	
IV. Whole analysis:	
(a.) reversal – simple and complex	
(b.) misplacements – simple and complex	
V. Process analysis:	
(a.) substitutions	
(b.) additions	
(c.) omissions	
Categories for Block Design Subtest	
VI. Unit analysis:	
(a.) unit rotation	
(b.) unit simplification	
(c.) unit distortion	
VII. Whole analysis:	
(a.) whole rotation	
(b.) whole simplification	
(c.) whole distortion	
VIII. Process analysis:	
(a.) simple-block placements	
(b.) multiple-block placements	

call with experimentally offered interfering stimuli is tested: analysis is focused on six classes of error: distortion, rotation, perseveration, omission, size, and misplacement. Frequency and severity of errors are noted.

Results indicate that the dysfunctions most clearly seen in the exposed group are disturbed memory and difficulty in maintaining alertness and appropriate focusing of attention. There is more usage of a variety of such compensations as delay, avoidance, inappropriate giving up, and slowing down among the exposed group. These findings are in contrast to those in unexposed controls, where failures usually take the form of incorrect answers, misinformation, and task inability at a stable and appropriate level. Precise relationships to work history, ChE levels, severity, and type and duration of exposure are not yet available.

Interviews are used as an independent check on some of the results of psychological testing and for the special information that can be gathered only in this way. The aim is to obtain a systematic and relatively objective view of exposed men's feelings about themselves, their symptoms (if any), changes over time of which they may be aware, and their attention to industrial health practice, for example. Men with histories of multiple or severe exposure complain directly and give evidence of being slowed down and less energetic and of having increasing memory difficult and greater irritability than the minimally exposed group (see TABLE 3).

Neurological examinations have been given to an approximately equal number of highly exposed and minimally exposed workers. There is no difference between the groups in terms of such hard neurological signs as sensory or motor deficits. It is our impression that exposed men show more so-called "soft" neurological signs such as minor coordination deficits and oculomotor imbalance. It is evident that the principal findings in neurological examination are slowness of thinking and calculation and memory deficit.

Electroencephalograms have been done on all men in the current study. Men with histories of OP exposure do not show the typical minimal changes we have found among individuals with chronic chlorinated hydrocarbon (CH) exposure. Chronic CH exposure tends to lead to EEGs that are low-voltage, fast, and poorly organized, with group trends toward a higher-than-expected incidence of minor abnormalities. The OP group exhibits contrast by virtue of higher voltage EEGs, with more adequate and distinct maintenance of the normal alpha rhythms.

The autocorrelogram is a transform of the EEG, or any other random time series data, by means of which it becomes possible to examine for periodicity within otherwise random data. Detailed descriptions of the methodology are available elsewhere (Metcalf & Hubbard, 1967; Hubbard, 1966). EEGs are tape-recorded and subjected to visual evaluation from direct write-out and computer analysis from FM magnetic tape (see FIGURE 2). A typical autocorrelogram derived from a 10-second EEG epoch consists of a periodically recurring sinus-

TABLE 3

INTERVIEW DATA REPORTED BY HIGH EXPOSURE VERSUS LOW EXPOSURE MEN

	High Group	Low Group
Nervousness and/or irritability	9	2
Changes in memory	9	3
Changes in sexual habits (increase or decrease)	6	0
Changes in sleep habits	5	1
Increased fatigability	8	4

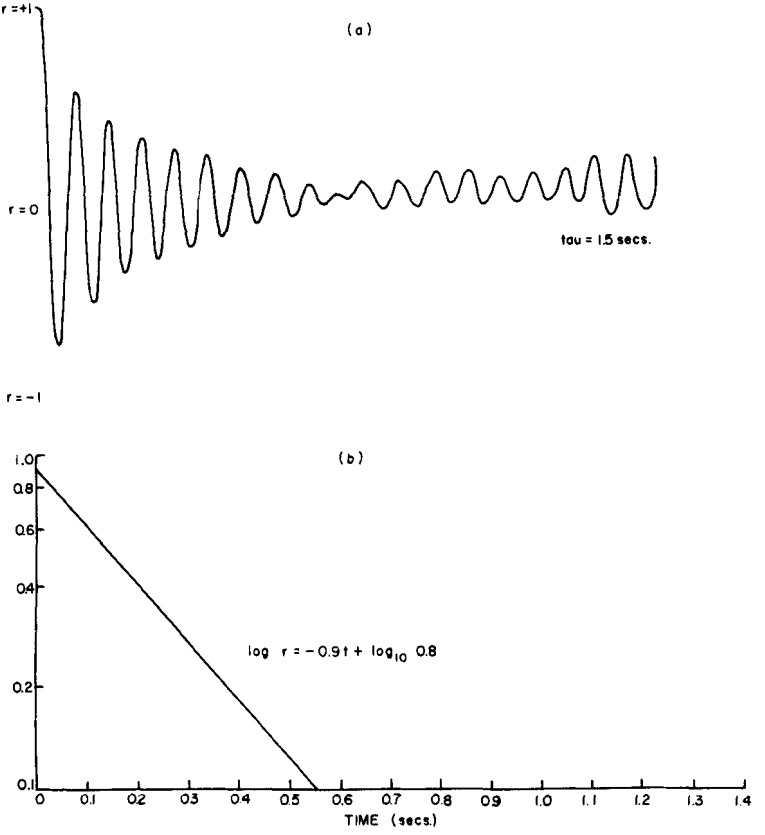

FIGURE 2. (a) Autocorrelogram of fairly well-organized, normal, awake EEG (parieto-occipital recording). (b) Log transformation to best fit straight line ("k" = −0.9).

oidal wave form whose repetition rate with progressive time delay (tau or τ) is representative of the dominant frequency of the EEG and whose progressive amplitude decrement with tau is related to the periodicity in the EEG. The autocorrelogram rate of decay is expressed by the equation

$$y = ae^{-k\tau}$$

Our best current data bearing on this point are derived from autocorrelation analysis of EEGs, using a special-purpose correlation computer.* Subjects were 50 men exposed to both CH and OP compounds. It was previously established that exposure to CH had no effect on the EEG, as described by these analytic methods. Data were then examined for OP effect by means of a linear regression analysis plotting history of OP exposure against the exponent k. A significant relationship is found between posthyperventilation EEG and differential history of OP exposure; individuals with higher OP exposure have EEGs with more rapid auto-

* This autocorrelation analysis was performed by Mr. Robert Hubbard, Chief, Data Reduction and Instrumentation Program Area, Tropospheric Telecommunications Laboratory, Institute for Telecommunication Sciences and Aeronomy, Environmental Science Services Administration (formerly U. S. National Bureau of Standards), Boulder, Colorado.

correlogram decay, i.e., less rhythmic EEGs. It was further found that the loss of rhythmicity was due to an increase in random slowing in these EEGs.

There is no increase in the incidence of hard EEG abnormalities such as spike activity or focal slowing. The outstanding finding in the EEG study is a high incidence of low- to medium-voltage slow activity in the Theta range, that is, 4 to 6 H_z activity occurring during light drowsiness in brief episodes of 2 to 4 seconds' duration (see FIGURE 3). This is a minimal type of EEG disturbance, but it mirrors, to a lesser degree, the more severe EEG disturbances seen after acute exposure. We have had the opportunity in one case (Holmes *et al.*, 1967) to follow for one year the natural history of this type of activity with serial EEGs starting after exposure. The gradual decline, but long persistence, of this fairly specific EEG sign enabled us to discover it in the old EEGs, as well as to recognize its presence in many current EEGs. It is not unlikely that computer analysis using recently developed methods would yield specific information permitting the rapid identification of changes and permit the EEG to be used as a sensitive early index of CNS impairment.

Visual and auditory evoked responses using a summing computer have been done on all men in the study population because of our hypothesis that OP exposures might result in disturbances of CNS information-processing capability. Sensory evoked responses are technically easy to gather, provide a large amount of information, and can be accomplished quickly, with large numbers of people and minimal facilities. Auditory evoked responses show more variability than the visual responses. Both show trends toward lower amplitudes and longer peak latencies in the exposure group, thus tending to support the initial hypothesis.

A special EEG study of all-night sleep was accomplished because of interview data indicating a high incidence of lethargy, drowsiness, sleep problems, and narcolepticlike symptoms. The all-night method was chosen because it could provide objective data on these subjective complaints. It is now generally recognized that individuals with narcolepsy show an unusual distribution and control of the various sleep stages through the night, particularly in the first two hours of sleep (Rechtschaffen, 1963). Narcoleptics often have distinctive eye-movement periods upon first falling asleep. Nine of our twelve subjects showed narcoleptic sleep records, and two demonstrated disturbances of the normal cycling of sleep stages through the night, as evidenced by unusually long stage I sleep—episodes up to 1½ hours in length. These findings suggest that complaints of excessive drowsiness relate to a demonstrable underlying disturbed physiology.

We speculate that the central effects of OP exposure are causally related to specific impact of OP compounds on deep midbrain, AChE-rich pontine centers. It is known that control of sleep-wake cycling is partially dependent upon ChE-AChE mechanisms (Hernandez-Peon, 1965); that specific sleep stages are under the influence of the mid and rostal pons (Jouvet, 1965); and that these structures are partially responsible for modulation of transmitted sensory input to the cortex. The specific EEG findings, sensory-evoked response disturbances, sleep disturbances, and nonspecific intellectual deficits all are compatible with the hypothesis that deep midbrain effects of OP-anticholinesterase compounds are of major importance in the production of the CNS changes we describe. Exposure to combinations of OP and CH agents may result in potentiation of the effects of either or both compounds. This effect may be attributed in part to CH-induced local AChE-ChE disturbance mediated via rupture of synaptic vesicles, as suggested by Albert (1965), in combination with central and systemic effects of OP anticholinesterase activity. Both of these central mechanisms may be relatively

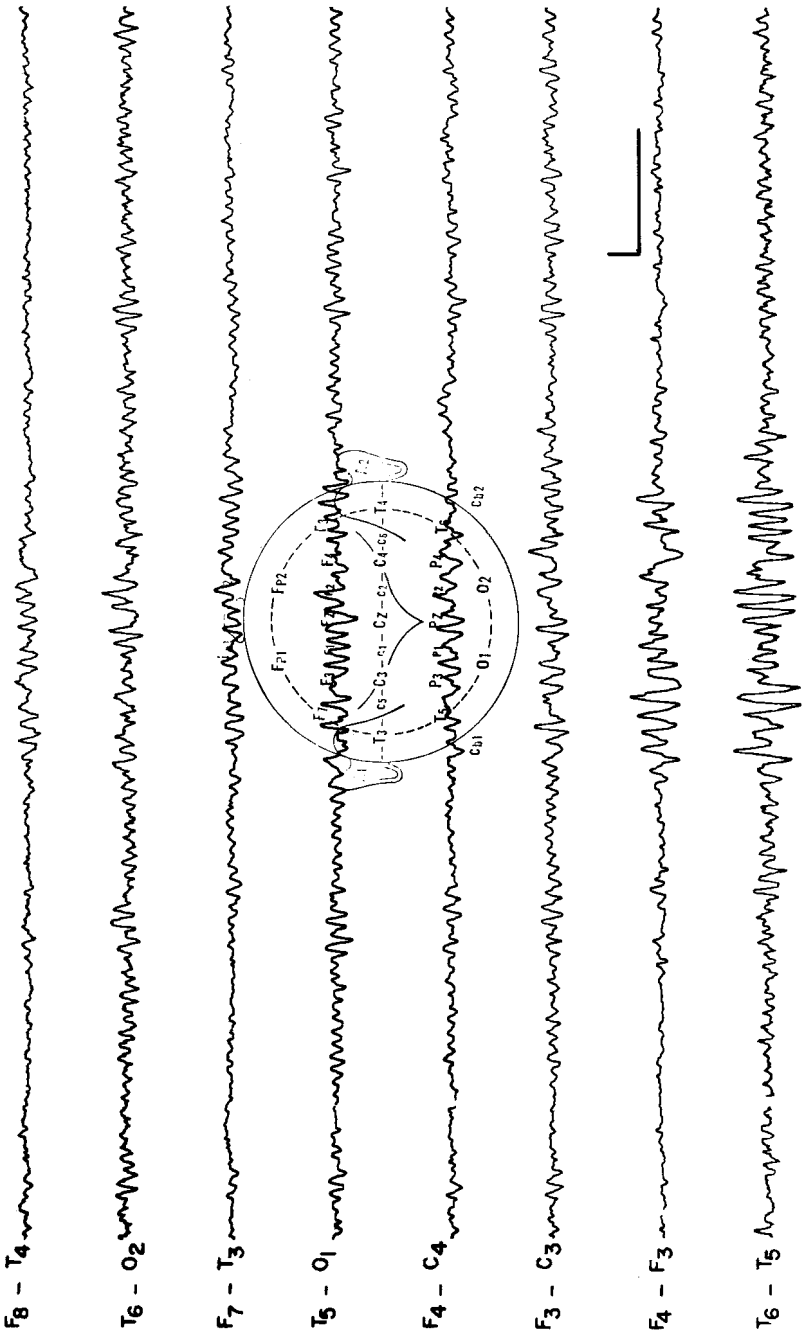

FIGURE 3. Typical chronic OP exposure.

resistant to pharmacological attack; it has been stated (Koelle, 1965) that the commonly used ChE reactivators such as 2-PAM do not effectively act at central synaptic sites. It appears, therefore, that there is need for further intensive study because of the unknowns we now recognize and because of the possibility that long-term exposure to OP compounds can induce irreversible or only slowly reversible brain dysfunction.

Acknowledgments

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