Electrophysiological findings in diphenyl poisoning

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SYNOPSIS The fungistatic agent diphenyl caused fatal poisoning with signs of neurotoxicity in a worker in a Finnish paper mill. This initiated a neurophysiological study of 24 workers occupationally exposed to diphenyl. Ten men showed EEG abnormalities, mainly diffuse or generalized ones. The abnormalities persisted on re-examination one and two years later. Nine subjects had EMG abnormalities; seven also exhibited fibrillations in some muscles. One subject showed a long rhythmic series of fasciculations similar to the spontaneous activity described in infantile spinal muscular atrophy. Nerve conduction velocity, especially that of slower motor fibres, was reduced in several cases. Electroneuromyographic abnormalities also persisted on re-examination. Although diphenyl is considered a comparatively safe chemical, it showed evidence of neurotoxicity when workers were exposed to concentrations in excess of the presently accepted threshold limits. Electrophysiological methods should be applied for the early detection of occupational hazards.

The fungistatic agent diphenyl is used as a preservative for citrus fruits. As a rule, it is impregnated into the wrapping paper in paper mills, where workers are exposed to varying degrees of concentration in a number of operations. It has been stated that diphenyl is a substance of fairly low toxicity (*Hygienic Guide Series, Diphenyl*, 1964; Weeks and Lentle, 1970). In experiments with rats and mice, prolonged exposure to diphenyl in air (5, 40, and 300 mg/m³) has produced liver and kidney injury (Deichmann *et al.*, 1947). Moreover, the prolonged consumption of food with a diphenyl content of 0.5 and 1% may result in kidney injury (Booth *et al.*, 1961). With human beings, only transient symptoms of nausea, vomiting, and bronchitis had been observed in some workers engaged in the impregnation of wrapping paper with diphenyl (Weil *et al.*, 1965), until several cases of diphenyl poisoning in a Finnish paper mill were described (Häkkinen *et al.*, 1973). The neurotoxic effects of diphenyl have been summarized in an earlier publication (Häkkinen *et al.*, 1973), but the present study gives a detailed description of neurophysiological findings in relation to diphenyl exposure.

METHODS

The process of impregnating wrapping paper with

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diphenyl, as well as concentrations in the air at various locations, have been published previously (Häkkinen *et al.*, 1973). It was noted that the exposure greatly exceeded the present TLV of 1 mg/m³. The average concentrations measured in the air at various work places varied from 0.6 to 123.6 mg/m³.

A total of 31 men were engaged in the process. In addition to these, it was suspected that two other workers, a stock keeper and a female paper cutter, were suffering from poisoning. The present study was initiated when one of the workers suddenly died, with symptoms of acute poisoning. As neurological signs were also apparent in this fatal case, it was decided that 24 workers of the above group would be subjected to neurophysiological tests; the 24 were those undergoing the heaviest exposure and/or those who had on medical examination revealed symptoms or signs suggestive of poisoning. Four of them were oilmen, 11 paper-machine workers, three rolling-machine workers, three men handled residue mass, one was engaged on maintenance, one was a stock keeper, and the only female was a paper cutter.

The commonest subjective symptoms were headache, gastrointestinal complaints (diffuse pain, nausea, indigestion), numbness and aching of the limbs, and general fatigue. One man of 27 years had twice lost consciousness while working, but denied that he had experienced spontaneous convulsive attacks.

All of the subjects underwent electroencephalographic (EEG) and electroneuromyographic (ENMG) studies, and 11 and seven men were subjected to re-examination after one and two years respectively. The exposure to diphenyl was stopped immediately after the first examination.

EEGs were registered for 30 minutes with an 8-channel Elema Mingograph, using hyperventilation for three minutes and photic stimulation as activa-

tion. Twenty-one silver-silver chloride electrodes were applied in accordance with the international 10-20 system (Jasper, 1958) and kept in place with a rubber net. An electrode jelly was used. Use was made of both scalp-to-scalp montages and montages with the ear electrode as reference.

The maximal motor conduction velocities of the median, ulnar, deep peroneal, and posterior tibial nerves were measured by conventional methods

FIG. 1 EEG of a male (29 years) with diphenyl poisoning. Bilateral spike and wave discharges. Montage indicated in the figure.

FIG. 2 Spontaneous serial electrical activity in the anterior tibial muscle of a male (55 years) with diphenyl poisoning.

(Cohen and Brumlik, 1968) with a Disa electromyograph and a Disa Multistim, with skin electrodes for both recording and stimulation. The latencies were read direct with the aid of a Multistim potentiometer. The conduction velocity of the slower motor fibres (CVSF) of the ulnar nerve was measured by application of the antidromic blocking technique described by Hopf (1962), slightly modified in our laboratory (Seppäläinen and Hernberg, 1972). The electromyogram of four to 10 muscles was studied with concentric needle electrodes and the Disa electromyograph. Attention was paid to voluntary activity, and to possible spontaneous activity.

RESULTS

ELECTROENCEPHALOGRAPHY Ten men of the 24 workers were found to have abnormal EEGs at the first examination. Six of them had diffuse slow wave abnormalities, two distinctive bilateral spike and slow wave discharges (Fig. 1) (one of them was the case with attacks of unconsciousness while working), one young man (age 24 years) had posterior slowing only, and a 60 year old man showed a mild slow wave abnormality in the right temporal area. Six men (aged from 27 to 55 years) displayed unusual distribution of alpha rhythm, with alpha activity also prominent in the frontal areas. This homogenization of the alpha activity was observed twice with diffuse slow wave abnormalities, and in four cases without EEG abnormalities.

At re-examination, normal EEGs remained normal; the diffuse abnormalities also stayed similar, but the two men with spike and wave discharges in the first recording began to show both diffuse slow wave abnormalities and spike and wave discharges. The mild temporal local abnormality was not noted at re-examination one year later. No actual improvement in the EEGs of seven men was discernible during an observation period of two years.

ENMG EXAMINATIONS It was considered that nerve conduction velocities had slowed down if they were less than the mean -2 standard deviations calculated from a population of 120 normal control persons from 20 to 60 years of age. As a rule, the maximal motor conduction velocities were decreased no more than slightly, but in the conduction velocity of the slower motor

TABLE 2
ENMG FINDINGS OF 24 SUBJECTS EXPOSED TO DIPHENYL

	MCV + CVSF normal	CVSF abnormal	MCV abnormal	MCV + CVSF abnormal
EMG normal	11	3	—	1
Motor unit changes	—	1	—	1
Fibrillations + motor unit changes	2	3	2	—

TABLE 1

NERVE CONDUCTION VELOCITIES OF 24 PERSONS EXPOSED TO DIPHENYL, AND OF 60 NORMAL MALES

Nerve	Diphenyl group (m/s)		Control group (m/s)		t-test
	mean	SD	mean	SD	
Median MCV	57.7	6.3	58.0	3.8	NS
Ulnar MCV	56.3	4.6	56.6	4.0	NS
CVSF	41.4	5.2	45.5	3.2	4.19 ($P < 0.001$)
Deep peroneal MCV	50.2	5.4	50.3	3.5	NS
CVSF	37.7	3.9	38.2	5.6	NS
Posterior tibial MCV	43.4	3.9	42.4	4.7	NS

MCV: maximal motor conduction velocity.

CVSF: conduction velocity of slowest motor fibres.

fibres (CVSF) the decrease amounted to as much as 25%. At the first examination, some MCV was found to have slowed in five men out of 24, but the CVSF of the ulnar nerve was slowed in nine men.

The mean MCVs of the diphenyl group did not differ from the mean values of 60 healthy Finnish males (Table 1). Quite frequently, the standard deviation was greater in the exposed group, thereby indicating a wider variation in individual values. Only the CVSF of the ulnar nerve in the diphenyl group was significantly slower than in the control population. Other studies have indicated that this factor is a sensitive measure of nerve dysfunction (Seppäläinen and Hernberg, 1972).

In the longitudinal follow-up of 11 patients, no significant change in the conduction velocity measures became apparent during the course of one year. When the results of the first examination were compared with those obtained two years later, the MCVs of the median and the deep peroneal nerves were found to be significantly slower ($P < 0.02$ and $P < 0.01$ respectively, $N = 7$) at the second re-examination.

Electromyographic examination revealed abnormal findings in 10 subjects, all of whom showed a diminished number of motor units on maximal contraction—that is, single units or mixed pattern, and often with units of long duration. Seven men also had fibrillations in some muscles. Usually, the men with abnormal EMGs displayed slowing of some nerve conduction velocities (Table 2).

Peculiar spontaneous activity was observed in the anterior tibial muscle of one 55 year old man. This activity (Fig. 2) appeared in rhythmical series lasting up to several minutes, a finding that was constant at both re-examinations. The potentials, probably fasciculations, up to $400 \mu V$, had a duration of up to 10 ms, and came at intervals of 20 to 30 ms. Two or three types of potentials could appear in a series at the same recording site, with each potential appearing at its own constant repetition rate. When he was subjected to operation by reason of symptoms of sciatic type, he was found to have atrophic nerve roots, but no protruding intervertebral discs.

At re-examination one year later, five out of 11

subjects showed increased ENMG abnormalities; in two, the abnormality had diminished in extent, and in four, one of whom had normal findings, the ENMG remained unchanged. At the end of two years, three men displayed diminishing ENMG abnormalities, three remained unchanged, and in only one case had the abnormality increased. The last-mentioned case now displayed signs of latent diabetes. The ENMG findings thus remained abnormal as well; they seemed to reach their maximum after the cessation of exposure during the one-year follow-up.

On combination of all the findings in the first examination, only five subjects—one woman and four men—were found to have perfectly normal records (Fig. 3). Very often the subjects had findings suggesting dysfunction both in the peripheral nervous system (ENMG) and in the central nervous system (EEG), if account is also taken of the abnormal distribution of alpha activity.

DISCUSSION

Although abnormal neurophysiological findings were very frequent among workers exposed to diphenyl, it needs to be borne in mind that the exposure was highly in excess of the currently accepted threshold limit value (TLV) of 1 mg/m^3 . The EEG abnormalities were mainly diffuse slow wave abnormalities; moreover, the two men with spike discharges displayed diffuse slow wave abnormalities at the follow-up examinations. This is nonspecific, but compatible with generalized cerebral disturbance. In a young person, the posterior slowing of EEG rhythms can also indicate generalized involvement since, at a lower age, slowing is often more pronounced in the posterior areas. The paroxysmal abnormalities (bilateral spike and wave discharges) could also indicate generalized cerebral disturbance in a person with lowered seizure threshold.

The ENMG abnormalities were always compatible with neurogenic disorders. The conduction velocities of the peripheral nerves were often decreased, thereby suggesting neuropathy. The slowing of the CVSF is normally observable in partial damage to the nerves, as in segmental demyelination. The spontaneous serial fascicula-

FIG. 3 Combinations of electrophysiological abnormalities of 19 subjects occupationally exposed to diphenyl. (Five subjects had normal records.)

tions noted in one man could have originated from a higher level, from the lower motor neurone in the spinal cord, resulting in atrophic nerve roots. Similarities are apparent between these fasciculations and the spontaneous activity described by Buchthal and Olsen (1970) in infantile spinal muscular atrophy. Furthermore, a lesion in the lower motor neurones cannot be excluded in the cases with abnormal EMG and normal conduction velocities.

Consequently, diphenyl attacks the human nervous system at several levels. The sites of greatest vulnerability are the brain and the peripheral nerves. The damage noted in the present study was minor in degree, amounting to slight diffuse involvement of the brain and partial neuropathy; however, these signs were quite persistent. Moreover, several of the patients continued to exhibit considerable incapacity, and subjective symptoms.

The chemicals utilized in industry may result in unfortunate consequences such as those described here, although these materials have been regarded as rather harmless. Neurotoxic symptoms may remain unnoticed in animal experiments if these are not specifically aimed at the investigation of nervous effects. Effects may not be the same in different species of animals or in human beings. In modern industry, one of the commonest hazards is the neurotoxicity of the materials used. If early symptoms are to be revealed, neurophysiological methods should be applied in the investigation of occupational diseases. Furthermore, neurophysiologists and

neurologists should call to mind the possible role of environmental noxae when neurological symptoms of unknown aetiology are found.

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