Neuromuscular function in pesticide workers

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Neuromuscular function in pesticide workers. Electromyography (EMG) provides a sensitive,
objective, and speedy method of detecting impairment of nerve and muscle function in
pesticide workers who are apparently in good health. Exposure to two organophosphorus
compounds (both were dimethyl phosphate esters) was associated with a high incidence
(about 50%) of EMG signs of impaired nerve and muscle function. In workers exposed only to
organochlorine compounds there was a much lower incidence (about 4%) of abnormal EMG.
Exposure to these organophosphorus compounds was not associated with depression of
blood cholinesterase activity even in those workers with typical EMG signs. It is concluded
that measurement of blood cholinesterase activity does not provide a sensitive index of
functional impairment of nerve and muscle.

Recent investigations by Roberts and Wilson (1969) on patients with myasthenia gravis have shown that
the electromyographic (EMG) response to nerve stimulation can be used to facilitate diagnosis and
control of anticholinesterase therapy. These studies have also shown that overdosage with neostigmine
or pyridostigmine can be detected by a number of abnormal features recorded in the EMG which
can be observed in patients who do not show typical signs of overtreatment other than a failure to respond
to periodic increases in daily dosage.

We have now used this method to determine whether there is evidence of functional abnormality
of nerve and muscle in workers exposed to high concentrations of organophosphorus (dimethyl
phosphate esters) and organochlorine pesticides. The current methods of monitoring these workers
consists of periodic determination of whole blood cholinesterase activity, to detect undue exposure to
organophosphorus compounds, and estimations of blood concentrations of organochlorines.

Subjects and methods
These workers were engaged in the manufacture and
formulation of pesticides at Shell Nederland Chemie,
N.V., Rotterdam, Holland. They were 66 men with
different degrees of exposure to organophosphorus and
organochlorine compounds (see Discussion for scientific
names), as follows:

Group I Thirty-six workers were exposed to organo-
phosphorus and organochlorine compounds in the
formulation plant.

Group II Twenty-four workers had a history of pro-
longed exposure to organochlorine compounds only.

Group III Control studies were made of 28 male
workers in the Pernis oil refinery who had never been
exposed to pesticides in the course of their work.

Group IV Six workers, not normally engaged in
pesticides, received one acute exposure to an organo-
phosphorus formulation.

Each subject visited the medical department of the
Shell Refinery during his working shift; the nature of his
work was not revealed until all the EMG results had been
assessed; the examination, consisting of electro-
myography and venous blood sampling, lasted about
20 minutes.

The electromyographic method used is illustrated in
Figure 1. It involves the use of surface electrodes for ulnar nerve stimulation and electrical recording of action potentials from the adductor pollicis muscle, and it has been fully described by Roberts and Wilson (1969).

Samples of venous blood were collected in bottles containing sodium heparin; aliquots were used to determine whole blood cholinesterase (blood ChE) by the method of Michel (1949).

![Diagram](image)

**FIG. 1.** Diagram of the electromyographic method used to study neuromuscular function in myasthenic patients and pesticide workers. The ulnar nerve is stimulated four times at quarter second intervals and the resultant muscle action potentials are amplified and displayed on an oscilloscope and on an ink-writer. The records shown in this figure were obtained from a normal subject.

**Results**

One of the characteristic features of the EMG response associated with overtreatment with carbamate anticholinesterases (neostigmine and pyridostigmine) as seen in myasthenic patients consists of low voltage potentials with repetitive activity (Fig. 2). A further feature of the EMG response during anticholinesterase overtreatment is related to the amplitude of the EMG potential evoked by nerve stimulation after a short period of voluntary activity in the muscle under test (the adductor pollicis). Under conditions of either optimal or under treatment, the amplitude of the first potential in a train of four is the same, or slightly larger, after voluntary activity than it was before the activity. When overtreatment has taken place, the first potential of the train is reduced in amplitude after voluntary activity. This effect is best seen when the EMG is recorded 3 to 5 seconds after the end of the voluntary activity, and gradually disappears over the next 10 to 15 seconds. This depression of the first potential increases as overtreatment continues, but decreases again following withdrawal of treatment (Fig. 3). In the light of these findings, the pesticide workers were examined electromyographically for similar signs of impaired neuromuscular function.

![EMG records](image)

**FIG. 2.** EMG records obtained from a myasthenic patient (A) while overtreated and (B) after reduction of the daily dose of pyridostigmine (Mestinon). Record (A) shows certain features associated with overtreatment, *viz.*, low voltage potentials and repetitive muscle activity after each stimulus.

![EMG records](image)

**FIG. 3.** EMG records obtained from a myasthenic patient (A) while optimally treated, and (B) during a period of overtreatment. In each case record 1 was made before, and record 2 after, a 10-second period of voluntary activity in the adductor pollicis muscle. During overtreatment the EMG potentials are smaller, the progressive decline in amplitude is more marked, and after voluntary activity the first potential of the train is reduced in amplitude.
Workers exposed to organophosphorus and organochlorine pesticides

Of the 36 workers in group I, 17 had EMG responses very similar to those found in mild myasthenic patients overtreated with carbamate compounds. A typical example is shown in Fig. 4, together with corresponding records from a worker in the control series. The records from the organophosphorus worker show some degree of repetitive activity, depression of the first potential after voluntary activity, and lower amplitude potentials. A summary of the data obtained in respect of these findings in the 17 workers in group I is shown in Table 1, together with those of the control group III. It will be seen that repetitive activity was observed in the records of 16, and, after voluntary activity, depression of the first potential occurred in 14, whereas these features were not observed in any of the control group. The mean amplitude of EMG potentials was 10·0 mV ± 1·2 in the 17 group I workers compared with 12·0 mV ± 1·0 in the group IV subjects. Records were also obtained later of 28 men in Liverpool who were members of the University Academic and Technical Staff in the same age groups as those of the Pernis control series; the mean EMG amplitude was 12·0 mV ± 0·6 and none showed any evidence of repetitive activity or of depression of the first potential after voluntary activity.

Observations were made on 6 of the 17 workers with abnormal EMG records at the beginning and at the end of a five-day working period, and these showed a progressive impairment of neuromuscular function during this time. At the start of a new shift, there were already signs of impaired neuromuscular function, viz., repetitive activity, depression of the first potential after voluntary activity, and low voltage; after five days' exposure to organophosphorus formulations, the EMG amplitudes had decreased further as shown in Table 2.

Workers exposed to organochlorine pesticides only

The records of the 26 workers in group II showed in only one case evidence of repetitive activity and depression of the first potential after voluntary activity. The mean amplitude of EMG potentials in this group was 11·7 mV ± 1·3 (Table 3 and Fig. 5).

EMG abnormalities in different groups of workers

Using the features described above as criteria of abnormality of EMG response, the records of all the workers were examined for evidence of impaired

![Fig. 4. EMG records from (A) a worker engaged on organophosphorus formulation and (B) a non-pesticide worker in the control group. In each case record 1 was made before, and record 2 after, a 10-second period of voluntary activity in the adductor pollicis muscle. Note in record (A) the low voltage potentials, the repetitive response to each stimulus, and the depression of the first potential in the train after voluntary activity.](image-url)

<table>
<thead>
<tr>
<th>Group I OP + OC</th>
<th>Repetitive activity</th>
<th>% Decrease in EMG voltage after voluntary activity</th>
<th>EMG amplitude (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Present</td>
<td>0</td>
<td>9·5</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0</td>
<td>11·0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>6</td>
<td>9·0</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>3</td>
<td>11·0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>12</td>
<td>11·0</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>10</td>
<td>10·0</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>5</td>
<td>12·0</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>10</td>
<td>8·3</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>6</td>
<td>11·5</td>
</tr>
<tr>
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<td></td>
<td>13</td>
<td>8·0</td>
</tr>
<tr>
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<td>10</td>
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<td>12</td>
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<td>10</td>
<td>9·5</td>
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<td></td>
<td>9</td>
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</tr>
<tr>
<td>14</td>
<td></td>
<td>10</td>
<td>7·7</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>0</td>
<td>10·0</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>12</td>
<td>9·6</td>
</tr>
<tr>
<td>17</td>
<td>Absent</td>
<td>10</td>
<td>11·2</td>
</tr>
</tbody>
</table>

10·0 ± 1·2 (Mean ± 1 SD)

<table>
<thead>
<tr>
<th>Group III 28 controls</th>
<th>Absent</th>
<th>None</th>
<th>12·0 ± 1·0 (Mean ± 1 SD)</th>
</tr>
</thead>
</table>

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**TABLE 1**

**ANALYSIS OF ABNORMAL EMG RECORDS FOUND IN 17 OF THE 36 ORGANOPHOSPHORUS AND ORGANOCHLORINE WORKERS IN GROUP I (OP + OC) COMPARED WITH GROUP III (CONTROL) WORKERS**

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neuromuscular function and a summary of the results is set out in Table 3. This shows that, of the workers chronically exposed to organophosphorus and organochlorine compounds (group I), nearly half showed some EMG signs of impaired function. By contrast, only one of those exposed only to organochlorines (group II) had abnormalities of EMG response. The amplitude of EMG potentials of the workers in groups I, II, and III are displayed graphically in Figure 5. There is no apparent difference in range and distribution of amplitudes of groups II and III; in group I, however, it will be seen that the values for 17 workers with abnormal EMG (Table 1) are in general lower than the others in this group.

Figure 6 shows the individual values of whole blood cholinesterase activity found in each group and indicates also those with evidence of EMG abnormalities. It will be seen that there are no real differences between the values for blood cholinesterase activity in any of the groups and that except in one case (group I) there is no apparent relation between impaired neuromuscular function and blood cholinesterase activity in the organophosphorus group of workers.

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**TABLE 2**

<table>
<thead>
<tr>
<th>Subject</th>
<th>EMG amplitude (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before work</td>
</tr>
<tr>
<td>1</td>
<td>10-0</td>
</tr>
<tr>
<td>2</td>
<td>8-5</td>
</tr>
<tr>
<td>3</td>
<td>11-5</td>
</tr>
<tr>
<td>4</td>
<td>10-5</td>
</tr>
<tr>
<td>5</td>
<td>8-0</td>
</tr>
<tr>
<td>6</td>
<td>12-5</td>
</tr>
<tr>
<td>Mean</td>
<td>10-5</td>
</tr>
</tbody>
</table>

**FIG. 5.** Graphical analysis of the amplitude of potentials in EMG records of pesticide workers (groups I and II) and non-pesticide workers (group III). Each symbol represents one worker and a shaded symbol denotes repetitive activity and/or depression of the first potential after voluntary activity.

**FIG. 6.** Graphical analysis of whole blood cholinesterase activity of pesticide (groups I and II) and non-pesticide (group III) workers. Each symbol represents one worker and a shaded symbol denotes an abnormal EMG record.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. in group</th>
<th>No. with repetitive activity</th>
<th>No. with decrease in EMG voltage after voluntary activity</th>
<th>Mean EMG amplitude ± 1 SD (mV)</th>
<th>Total no. with abnormal EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I OP + OC</td>
<td>36</td>
<td>16</td>
<td>14</td>
<td>10.8 ± 1.3</td>
<td>17</td>
</tr>
<tr>
<td>II OC only</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>11.7 ± 1.3</td>
<td>1</td>
</tr>
<tr>
<td>III Controls</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>12.0 ± 1.0</td>
<td>0</td>
</tr>
</tbody>
</table>
Non-pesticide workers after a single exposure to a concentrated organophosphorus formulation (group IV)

During the course of these observations on chronically exposed pesticide workers, six workers with no previous industrial contact with pesticides were accidentally exposed to an organophosphorus formulation for a period lasting two to three hours. EMG tests carried out a few hours after exposure indicated some degree of functional neuromuscular impairment. As shown in Table 4, the EMG potentials were of low amplitude, there was repetitive activity in four workers, and in three, the first potential of the train was depressed after voluntary activity in the adductor pollicis muscle. Three of the workers were re-examined 48 hours later, by which time the EMG potentials were increased, and the first potential was not depressed after voluntary activity. Whole blood cholinesterase levels were measured at the times of EMG tests and, except in case 5, all were within the range found in the control series (Fig. 6).

Discussion

The results of this preliminary investigation show that, during the process of formulation of organophosphorus compounds, nearly half the workers in group I absorbed amounts of these compounds sufficient to produce abnormal EMG responses. A similar proportion of the workers in group IV were affected in the same way; here, however, the exposure occurred only once – accidentally – either while cleaning drums previously used to contain a mixed organophosphorus and organochlorine formulation, or while taking samples from full drums for a test analysis. The presence of organochlorine compounds in the formulations is unlikely to be an important factor contributing to these abnormal EMG responses since only one of 28 workers exposed only to organochlorine compounds had an abnormal EMG record.

Owing to the lack of suitably sensitive methods, it was not possible to measure blood and tissue levels of organophosphorus compounds and relate these to the degree of EMG abnormality found. That such a relation exists, however, is suggested by the increase in EMG abnormality during a five-day work period, and by the improvement noted after a period away from work.

Measurements of whole blood cholinesterase levels were made in an attempt to provide an indirect assessment of the rate of absorption of organophosphorus compounds. It had been hoped to use the degree of depression of enzyme activity as an indication of the concentration of organophosphorus compounds to which the tissues were exposed. However, in each group of workers a wide range of values was found, and the mean and standard deviations of the organophosphorus exposed groups did not differ significantly from those of the other groups. Whole blood cholinesterase measurement, which is the standard method of monitoring, gave no indication of these exposures to organophosphorus compounds, and there are a number of possible reasons for this lack of sensitivity.

In the first place, spontaneous fluctuations in enzyme activity occur in normal individuals, and in any group of normal subjects there is a wide range of values. Secondly, depression of whole blood cholinesterase activity by anticholinesterase compounds may be slower and less sensitive than that of plasma alone (Wilson, Maw and Geoghegan, 1951). Thirdly, organophosphorus levels in blood

TABLE 4

<table>
<thead>
<tr>
<th>Subject</th>
<th>EMG abnormalities</th>
<th>EMG voltage (mV)</th>
<th>Blood ChE (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Repetitive activity</td>
<td>%Depression after voluntary activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>b</td>
<td>a</td>
</tr>
<tr>
<td>1</td>
<td>Present</td>
<td>Absent</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>&quot;</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>n/e</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Absent</td>
<td>n/e</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>n/e</td>
<td>0</td>
</tr>
</tbody>
</table>

a = 2 to 3 hours after exposure.
b = 48 hours
n/e = not examined " " " "
are likely to be highest shortly after exposure, and to decline quickly as dilution occurs in the body fluids. It is unlikely, therefore, that a spot check of blood cholinesterase activity would reveal any depression unless the sample had been taken shortly after exposure. Holmes and Gaon (1956) have described some of the anomalies encountered in the interpretation of plasma and red cell cholinesterase values in men chronically exposed to parathion in aircraft spraying outfits. Ladell (1961) has also drawn attention to the phenomenon whereby ‘spontaneous reactivation of the blood cholinesterase does occur’, e.g., in parathion poisoning, in which the cholinesterase level in the blood after death was quite high, and suggested that brain cholinesterase may be reactivated more slowly than blood cholinesterase.

It is also possible that the abnormalities of nerve and muscle function detected electromyographically are not due directly to the inhibition of cholinesterase, but are the consequence of some other action of the organophosphorus compounds. For example, observations (unpublished) on myasthenic patients overtreated with pyridostigmine have shown that, after complete withdrawal of therapy, plasma cholinesterase returns to normal more quickly than the EMG response. This evidence is supported by the experimental results obtained by Roberts and Thesleff (1969), who reported that, in rats chronically treated with high doses of neostigmine, the resultant muscular weakness was associated with a diminished output of acetylcholine from motor nerve terminals, and that this effect was observed at a time when the plasma cholinesterase levels had returned to normal. Whatever the cause of the abnormal nerve and muscle action, its effect outlasts the depression of plasma cholinesterase. If recovery from organophosphorus exposure follows the same pattern, the longer duration of EMG abnormalities is likely to provide a more sensitive method for detecting the occurrence of exposure than can be obtained with the blood cholinesterase method.

In the present study, the organophosphorus compounds used in formulation were dimethyl vinylphosphates, namely, the cis-isomer of 3-(dimethoxyphosphinoxy)-N,N-dimethyl crotonamide (Bidrin) and the β-isomer of 2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate (Gardon). It will be important, therefore, to observe whether similar EMG abnormalities are produced by other organophosphorus compounds, and also by carbamates, in pesticides workers and sprayers engaged in handling these compounds.

Finally, it should be pointed out that all the workers examined, including those with EMG abnormalities, appeared to be in good physical condition, and none complained of any muscular weakness. They all had good muscular physique and were probably working well within their capacity. From this it is clear that electromyography provides a very sensitive early warning of exposure to organophosphorus compounds while pointing to the need for more fundamental studies on the nature and cause of the abnormal functional effects.

We are grateful for technical assistance to Miss van Eijk, Miss Geeratz, and Mr. Vermin at the Industrial Medical Department of Shell Nederland Raffinaderij, N.V.

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References


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