Electrophysiological and histological observations on peripheral nerves in acrylamide poisoning in man

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In 1967 Garland and Patterson described six patients who developed peripheral neuropathy and ataxia after exposure to acrylamide during their work. The neuropathy involved both motor and sensory fibres. Ataxia was out of proportion to the sensory loss and was thought to indicate brain-stem as well as peripheral nerve involvement by the poison. Electrophysiological studies of peripheral nerve conduction have been carried out on three of these patients and sural nerve biopsies on two of them. The findings form the basis of the present report.

A few other cases of industrial poisoning by acrylamide have been recorded. Ten cases were described by Fujita, Shibata, Kato, Amomi, Itomi, Sujuki, Nakajawa, and Tamahashi in 1960 from Japan, and a further case has been reported from Canada by Auld and Bedwell (1967). The clinical features of these patients were similar to those described by Garland and Patterson (1967).

METHODS

ELECTROPHYSIOLOGY Motor nerve conduction velocity was measured using standard techniques, muscle action potentials being recorded through a concentric needle electrode inserted into one of the small muscles of the hand or foot (Thomas, Sears, and Gilliatt, 1959).

Sensory nerve action potentials were recorded through sledge electrodes over the median or ulnar nerves at the wrist as described by Dawson (1956).

HISTOLOGY Biopsies of the sural nerve were taken at the level of the lateral malleolus at the ankle. Part of each nerve was fixed in Flemming's solution and transverse sections stained with Kulschitzky's haematoxylin (Gutmann and Sanders, 1943). Details of measurement of fibre diameter and estimation of density were similar to those of O'Sullivan and Swallow (1968). The rest of the specimen was fixed in 10% formol saline. After staining in 1% osmium tetroxide single fibres were isolated as described by Thomas (1955).

RESULTS

CLINICAL FEATURES The patients described here are Cases 1, 4, and 5 of Garland and Patterson (1967). The duration of exposure to acrylamide and of neurological symptoms for the three patients are shown in Table I. Two of them (J.B. and A.D.) rapidly developed severe symptoms after short exposure, but in the third patient (C.H.) abnormalities were less severe and developed slowly after longer exposure. All were recovering at the time of investigation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Garland and Patterson (1967) (Case no.)</th>
<th>Age</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.B.</td>
<td>1</td>
<td>19</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>A.D.</td>
<td>4</td>
<td>56</td>
<td>1½</td>
</tr>
<tr>
<td>C.H.</td>
<td>5</td>
<td>59</td>
<td>18</td>
</tr>
</tbody>
</table>

J.B. became severely disabled over the course of two months, after exposure to acrylamide for only one month before the onset of symptoms. When most severely affected he was just able to walk but fell frequently and was unable to drink from a cup. This was due to a combination of ataxia and weakness. At the time of investigation six months after removal from exposure he had improved considerably but still had some weakness of his hand muscles. He had severe bilateral foot drop and was slightly ataxic. Tendon reflexes were sluggish in the arms; ankle jerks were absent. There was no sensory abnormality.

A.D. became severely disabled within two weeks of the onset of symptoms, after exposure for only six weeks. At the height of the illness he was markedly ataxic, unable to walk without support and had sensory loss which caused him to burn himself without being aware of it. His symptoms slowly improved over the subsequent months. At the time of investigation, eight months later, he had mild limb...
ataxia without weakness. Tendon reflexes were all sluggish but present. There was partial loss of superficial sensation distal to the elbows and knees, vibration and position sense being normal.

C.H. had worked with acrylamide for 18 months before developing weakness and sensory symptoms in his hands and feet. These progressed slowly for two months and by the end of this time he was also ataxic. His symptoms were, however, less severe than those of the other two patients. He was recovering at the time of investigation 10 weeks later, when he still had mild distal weakness of the hands and feet, but was not ataxic. Tendon reflexes were absent. Superficial sensation was slightly impaired over the distal parts of his fingers and over his feet.

**Electrophysiology** The results of motor conduction studies are shown in Table II and Figure 1. Distal latency was within the control range in all instances except for the right lateral popliteal nerve of A.D. where a value of 7.5 msec was found—(control range: 4.9 ± 0.9 msec (Yap and Hirotu, 1967). Maximal conduction velocity was normal in 11 of the 14 nerves examined. In two cases values just below the control range were recorded and in only one instance was there a marked reduction of velocity. A value of 23.8 m/sec was found in one lateral popliteal nerve of C.H. There were only two or three surviving motor units in this nerve.

More striking than reduction in maximal conduction velocity was the dispersion of the muscle response to nerve stimulation. In many instances it was possible to identify late components in the dispersed responses; these late components appeared to be of constant waveform when the motor nerve was stimulated at different levels. After the responses to supramaximal stimulation had been recorded, stimulus intensity was varied to determine whether the late components had all-or-none responses— that is, whether they arose from single motor units with relatively long latencies. In many instances this appeared to be the case. Examples of delayed motor unit potentials are shown in Figures 2 and 3. In Fig. 2 the response to stimulation of the median nerve of C.H. shows a clearly recognizable late potential with stimulation at three levels in the arm, the distal latency being 17.0 msec, whereas the latency of the earliest unit to respond was 3.2 msec. Even greater dispersion of the muscle response to stimulation of the lateral popliteal nerve occurred in A.D. (Figure 3).

Conduction times over proximal segments were measured for late potentials in eight different nerves. In Fig. 4 these are compared with similar measurements for the earliest components of the response to nerve stimulation at each level. It can be seen that in all instances except one, the late motor unit potentials had distal latencies at least three times that of the early potentials, whereas proximal conduction times were only slightly longer. There was

![Graph showing maximal motor nerve conduction velocities in the forearm and leg for the acrylamide patients.](http://jnnp.bmj.com/)

**FIG. 1.** Maximal motor nerve conduction velocities in the forearm and leg for the acrylamide patients. The solid lines are mean control values and dotted lines are 2 S.D. from mean obtained by Thomas, Sears, and Gilliatt (1959).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Median nerve</th>
<th>Ulnar nerve</th>
<th>Lateral popliteal</th>
<th>Medial popliteal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>distal latency (msec)</td>
<td>forearm velocity (m/sec)</td>
<td>distal latency (msec)*</td>
<td>forearm velocity (m/sec)</td>
</tr>
<tr>
<td>J.B.</td>
<td>4.0</td>
<td>56.8</td>
<td>3.5</td>
<td>52.5</td>
</tr>
<tr>
<td>A.D.</td>
<td>3.2</td>
<td>63.9</td>
<td>3.2</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.H.</td>
<td>R 3.2</td>
<td>47.0</td>
<td>4.0</td>
<td>45.9</td>
</tr>
<tr>
<td></td>
<td>L 4.2</td>
<td>48.9</td>
<td>5.0</td>
<td>50.8</td>
</tr>
</tbody>
</table>

*Response recorded from first dorsal interosseous muscle.
thus disproportionate slowing of conduction in the
distal parts of these fibres. The most striking example
was in the lateral popliteal nerve of A.D. (Fig. 3),
the late potential having a distal latency eight times
that of the early response, whereas conduction time
in the leg was increased only by 30%.

In the left ulnar nerve of C.H. a single motor unit
potential with rather different characteristics was
identified. Conduction velocity showed little change
in the upper arm, but conduction time was con-
siderably prolonged in the forearm and elbow
segment as well as distal to the wrist. This indicates
an abnormality extending as high as the elbow.

When sensory conduction was studied no ascend-
ing action potential could be recorded from the
median nerve at the wrist with stimulation of the
digital nerves of the index finger in either A.D. or
J.B. A small action potential of 5 μV amplitude was
recorded from the median nerve of C.H.—control
range 9 to 45 μV (Gilliatt and Sears, 1958). These
findings indicate involvement of sensory fibres in
their peripheral parts.

HISTOLOGY Single fibres from the sural nerve of
A.D. and C.H. were examined. Sural nerves obtained
at necropsy from three control subjects aged 55 to 60

FIG. 2. Muscle action potentials recorded through a
concentric needle electrode in abductor pollicis brevis in
response to stimulation of median nerve at wrist, elbow, and
axilla.

FIG. 3. Muscle action potentials recorded through a
concentric needle electrode in extensor digitorum brevis
in response to stimulation of anterior tibial nerve at ankle
and lateral popliteal nerve at knee.

FIG. 4. Conduction times in different segments of nerve
for early and late potentials.
years were also studied for comparison. In view of
the pathological changes in peripheral nerves of
patients with extensive vascular disease described
by Chopra and Hurwitz (1967) and Eames and
Lange (1967), nerves from patients with severe
atheroma were not used in the present study.

No fibres in the process of degeneration were seen
in any of the control nerves or in the nerve from
A.D. This patient had not been exposed to acryl-
amide for eight months before the biopsy was
performed. C.H. had been exposed to acrylamide
more recently, until two and a half months before
biopsy. In his sural nerve a few fibres were seen to be
undergoing degeneration, the appearance being
similar to that of Wallerian degeneration.

Internodal length and fibre diameter of all the
single fibres were measured and the results are shown
in Fig. 5, presented as described by Fullerton,
few fibres from each of the control and acrylamide
nerves showed some evidence of previous segmental
demyelination by the presence of internodes of
irregular length along the same fibre. The incidence
of this type of abnormality was no greater in the
acrylamide than in the control nerves. It is interest-
ing, however, that these three control nerves
appeared to show rather more segmental demyeli-
ation than subjects of a similar age studied by
Lascelles and Thomas (1966).

Regenerating fibres may be recognized by having
uniformly shorter internodal lengths in relation to
diameter than normal fibres (Vizoso and Young,
1948). It can be seen from Fig. 5 that some large
diameter fibres from both A.D. and C.H. had
shorter internodal lengths than fibres of the same
diameter from the control nerves, suggesting that
they had degenerated and subsequently regenerated.
For example, among the single fibres isolated which
did not show segmental demyelination, there were
five from the nerve of A.D. and six from the nerve
of C.H. with a mean diameter greater than 8 μ.
that had a mean internodal length of less than 0.5
mm. No large diameter fibres with such short inter-
nodes were seen in the control nerves.

Quantitative studies were carried out on trans-
verse sections of sural nerve from C.H. The diameters
of over 800 myelinated fibres were measured and
density calculated. A histogram showing the dis-
tribution of fibre size is shown in Figure 6b. This

FIG. 5. Internodal length and fibre diameter for single
sural nerve fibres. Each dot represents one internodal
segment and segments from the same fibre are joined by
a vertical line. The diameter plotted for each fibre is that
of the largest segment on the fibre.
densities are within the control range but that the large fibre density is considerably reduced.

Unfortunately, only one small bundle containing 200 fibres was present in the transverse sections from A.D. and quantitative studies are not reliable on such a small number of fibres. There appeared, however, to be no gross abnormality.

In summary, the nerve from C.H. contained a few degenerating fibres and others which were thought to have regenerated. Evidence of regeneration was also present in the nerve from A.D. In one of the patients (C.H.) a significant loss of large diameter fibres was demonstrated in transverse sections.

**DISCUSSION**

Acrylamide is known to be neurotoxic to many species (Kuperman, 1958; McCollister, Oyen, and Rowe, 1964). Pathological changes in peripheral nerves of rats fed with acrylamide in their diet were described by Fullerton and Barnes (1966). These consisted of a dying-back process with fibre degeneration affecting first and most severely the distal ends of the longest fibres. No segmental demyelination was found in this species. More recently similar pathology has been demonstrated in baboons, but in this species paranodal demyelination was also seen (Hopkins and Gilliatt, 1967; Hopkins, in preparation).

Peripheral nerve conduction was studied in both these species. In severely paralysed rats, maximal motor conduction velocity was reduced by 20% and in baboons there was often a reduction of 30 to 40%. In the present study changes in maximal velocity were slight. These changes in maximal velocity in both man and animals are substantially less than those which may occur when segmental demyelination is present (Gilliatt, 1966; Morgan-Hughes, 1968). As far as sensory nerve conduction is concerned, Hopkins and Gilliatt (1967) found that action potentials disappeared in baboons during acrylamide poisoning. This finding is comparable with the observations on the patients reported here.

An interesting feature of the present study was the marked dispersion of the muscle responses to nerve stimulation. This appeared to be due to delayed conduction in the distal parts of some of the motor fibres, others being unaffected. This phenomenon is most likely to be an indication of regeneration, since conduction velocity is known to be as low as 5% of normal in the earliest stages of regeneration (Hodes, Larrabee, and German, 1948). If this be the correct explanation, then regeneration appears to be confined to the distal parts of the fibres. This would be expected in the early stages of recovery from a dying-back disease. Rather similar electrical
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findings have been seen during recovery from tri-ortho-cresyl phosphate neuropathy in baboons (J.E.C. Hern, personal communication).

It seems unlikely that the late muscle potentials were merely parts of motor units with lengthened duration due to collateral sprouting, since they appeared to have different thresholds from the early part of the muscle action potential. However, it is difficult to eliminate this possibility entirely. For example, Fullerton and Gilliatt (1965) demonstrated that axon branching could occur in peripheral nerve lesions in man and that the branches might terminate in widely separate parts of the muscle, so that the two components could not be recorded through a single coaxial needle electrode.

One other possible interpretation is that pressure might have produced localized nerve damage. In some conditions pathological nerves are known to be unduly susceptible to pressure, for example in diabetes (Mulder, Lambert, Bastron, and Sprague, 1961), some familial neuropathies (Earl, Fullerton, Wakefield, and Schutta, 1964), and experimental diphtheritic neuropathy (Hopkins and Morgan-Hughes, 1967). Compression in the carpal tunnel could explain the distal slowing in the median nerves. The finding that slowing extends as high as the elbow in one ulnar nerve of C.H. might add some support to this explanation, since pressure lesions at the elbow are common. However, in all the other fibres studied, including the other ulnar nerve of C.H., marked delay was confined to their distal parts regardless of whether or not these are common sites for pressure to occur. This explanation thus seems unlikely.

It is interesting that some fibres were found in the nerve biopsy specimen from C.H. with large diameters and short internodal lengths. Despite the fact that the biopsy was taken only two-and-a-half months after he stopped work, this suggests that regeneration was well advanced. It seems likely that regeneration was occurring while exposure continued and even before the patient had developed symptoms two months previously. In rat nerves Fullerton and Barnes (1966) also found evidence of regeneration while the animals continued on a low dose of acrylamide in their diet.

SUMMARY

Maximal motor nerve conduction velocity in three patients recovering from acrylamide neuropathy was normal or only slightly reduced, except in one nerve. The muscle response to nerve stimulation was usually dispersed and potentials with markedly prolonged distal latencies were found. It is suggested that the slow conduction is due to degeneration followed by regeneration of the distal parts of the fibres. Sensory nerve action potentials were reduced in amplitude or absent.

Pathological examination of sural nerves from two patients showed that segmental demyelination was no more common than in control nerves. Degenerating fibres were found in the patient most recently exposed to acrylamide and evidence of regeneration was found in both nerves. Correlation with the clinical course in one patient suggested that degeneration and regeneration began before symptoms developed.

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