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Toxic Chemicals and Peripheral Neuropathy

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Toxic Chemicals and Peripheral Neuropathy: Clinical and Epidemiological Features

A large number of substances are known to produce peripheral neuropathy but only those substances which are, or have been, a hazard in industry will be considered here. All the drug-induced neuropathies will be excluded except in so far as they illustrate some general principles.

Although there are many known toxic substances, it is easy to exaggerate their clinical importance for it must be remembered that in a substantial number of patients who develop peripheral neuropathy no cause is discovered, even after extensive investigations have been carried out. When this happens any chemical in the patient's environment can be a useful scapegoat; but some of the reports of neuropathy alleged to be caused by a particular chemical are not very convincing and once a substance has been blamed for a particular toxic effect the case against it may be self-perpetuating. Without denying the importance of reporting suspected toxic effects, even if not absolutely proven, it is vital that, from time to time, the evidence should be critically reviewed.

An example of too little suspicion about possible toxicity occurred last year, however, when several men were recognized to have developed acrylamide poisoning. Acrylamide has been known for over ten years to be neurotoxic (Kuperman 1958) and it causes an easily reproducible peripheral neuropathy in animals (Fullerton & Barnes 1966). The substance is now widely used in industry and yet a number of workers became severely disabled without acrylamide being recognized as the cause (Garland & Patterson 1967).

The substances which may be met in industry and which may cause peripheral neuropathy may be listed as follows:

I. *Peripheral neuropathy predominant:* Lead, acrylamide, organophosphates, thallium
II. *CNS involvement prominant:* Carbon disulphide, methyl mercury, methyl bromide
III. *Only after gross overdose:* Arsenic, trichloroethylene, tetrachlorethane, 2,4-D (dichlorophenoxyacetic acid), pentachlorophenol, DDT
IV. *Other systems more affected:* Carbon tetrachloride, carbon monoxide

These substances are surprisingly few in number. But substances about which the incriminatory evidence seems inadequate and also those which have not been referred to in the literature during this century have been omitted. It is useful to divide the toxic substances into different categories. For example, it is diagnostically important to separate substances whose main toxic effect is on the peripheral nerves from those that cause more widespread neurological damage. In the latter group, peripheral neuropathy may form a relatively insignificant part of the clinical picture. Furthermore, when considering whether a patient is likely to be suffering from a toxic effect it is useful to know whether the substance in question is a hazard in normal industrial use or whether poisoning only occurs after gross overexposure (Groups I and III). There can be no absolute distinction between these groups, however, since the care taken in using a substance will determine into which category it will fall.

Most toxic substances are thought to produce their effect by interfering with some aspect of cell metabolism even though the biochemical effect of many of the substances in the list is far from understood.

What criteria should one use to establish whether a patient is suffering from a neurotoxic effect? (*See* Table 1). The clinical picture may be characteristic. If a substance is to be blamed for a neurological disturbance the abnormalities should be similar to those previously described. For example, if a pure sensory neuropathy developed in a lead worker it is most unlikely to be due to his occupation. On the other hand, wrist drop is so classically associated with lead poisoning that no one should fail to enquire into the occupation of someone presenting with this symptom and no apparent cause for it.

Table 1
Criteria for establishing metabolic toxicity

Characteristic clinical features
Relation to exposure: individual susceptibility
Time relation
Reproducible in animals

Another example is industrial trichloroethylene. Cranial nerve damage may follow high exposure to this substance, although whether an impurity or breakdown product is actually responsible is less sure. A number of examples were described in the 1930s and have been well reviewed by Smith (1966). More recently Buxton & Hayward (1967) have described 2 patients who developed severe cranial nerve paralysis after working in a tank containing a high concentration of trichloroethylene. In these patients the peripheral nerves of the limbs were unaffected clinically. Feldman & Mayer (1968) have, however, described a similar patient with severe cranial nerve palsies in whom electrophysiological studies did show minor involvement of peripheral nerves. Nevertheless, if a worker exposed to this substance develops a distal limb neuropathy without cranial involvement it would be unwise to incriminate trichloroethylene.

In other instances the characteristic clinical features depend on a combination of CNS and peripheral involvement. For example, in carbon disulphide poisoning encephalopathy with prominent mental disturbances and parkinsonism are common (Vigliani 1954). In methyl mercury poisoning the peripheral nerve element is usually overshadowed by cerebellar and cortical abnormalities producing ataxia and blindness (Hunter *et al.* 1940). The clinical picture may not always be so specific and amongst the drug neuropathies, for example, there is little to distinguish between those produced by isoniazid and nitrofurantoin. They both produce a distal sensory neuropathy.

A clear case for implicating a substance as the cause of neuropathy can be made if the disorder is shown to occur predominantly amongst those with the highest exposure. The recognition that carbon disulphide may be neurotoxic is a good example. Poisoning became common when the viscose rayon industry expanded in Italy in the 1920s and 1930s. When the hazard was recognized steps were taken to reduce the degree of exposure and fewer cases occurred. During bad wartime conditions there were new outbreaks of poisoning in Italy and Poland and these have provided some valuable data about levels of exposure in relation to symptoms (Vigliani 1954, Paluch 1948). For example, Paluch (1948) found that 77 of 600 workers developed significant neuropathy in two years when exposed to 300–400 ppm in the atmosphere. On the other hand, Rubin & Arieff in 1945 examined 100 men who had worked in an atmosphere containing less than 30 ppm and found that vague symptoms were no more common than among a control non-exposed group of workers. This type of well-controlled negative survey is of great practical importance in getting the problems into perspective.

For some substances the onset of symptoms may not be solely related to the degree of exposure and in a few instances other factors are known to predispose to toxic complications. This is best illustrated by a well-known example of a drug neuropathy. Genetic factors are all-important in determining whether a patient taking isoniazid is likely to develop neuropathy. The population is divided into slow and rapid inactivators depending on the rate of acetylation by the liver (Evans *et al.* 1960, Evans 1963). Slow inactivators develop high blood levels of the drug and it is these people who are liable to develop neuropathy. A rather similar situation exists for another drug neuropathy, namely, nitrofurantoin. Neuropathy is rare except in patients with renal failure (Ellis 1962) and it has been demonstrated that impaired excretion in these people results in high blood levels of the drug (Loughridge 1962). Similar factors almost certainly exist in making some people more liable to industrial poisoning but at present little is known about these. This is a most important field in which there will surely be many advances in the future.

The time of onset of symptoms may give an obvious lead to their cause, particularly following accidents. For example, there are in the literature reports of 7 patients who developed neuropathy which seems reasonably attributable to dichlorphenoxyacetic acid, or 2,4-D as it is commonly called (Goldstein *et al.* 1959, Monarco & di Vito 1961, Todd 1962, Foissac-Gegoux 1962, Berkley & Magee 1963). This substance is a herbicide and poisoning in all instances followed exposure of the

skin to the liquid for many hours. A general illness developed within twenty-four hours and neurological symptoms a few days later.

It is likely that not all toxic neuropathies are the result of a direct biochemical effect and one should ask whether in some instances there may be an immunological basis involving some sort of antigen-antibody reaction. Little is known about immune mechanisms in the nervous system and at present there are no satisfactory techniques for investigating the problem. Suggested criteria for implicating an immune response in the development of neuropathy are shown in Table 2. To take further examples from the drug field, the peripheral neuropathy which may develop during a serum sickness reaction, particularly following antitetanus serum, undoubtedly has an immunological basis and it is worth briefly reviewing the typical clinical picture. The onset is abrupt, usually with severe pain; paralysis often affects proximal muscles, particularly of the upper limb, and is commonly asymmetrical. It seems possible that the neuropathy which occasionally follows gold and organic arsenic injections has a similar basis. Endtz (1958) summarized the picture of neuropathy following gold injections. The onset is usually abrupt and pain prominent. Weakness is often generalized but in some patients only one limb may be involved. Many of the patients have fevers and skin rashes at the same time. As for organic arsenic, 14 of 37 patients reviewed by Kellogg & Epstein in 1934 had exfoliative dermatitis at the time they developed neuropathy. Exfoliative dermatitis is not always an allergic phenomenon but Costello & Landry (1945) pointed out that amongst their 50 patients the only ones who developed this complication after the first injection in a course of treatment had had previous injections some years earlier. As in the case of gold, the onset of neuropathy following organic arsenic is abrupt and unrelated to dose. It is important to realize that this response to organic arsenic is different from the effect of inorganic arsenic, a commoner industrial problem. Inorganic arsenic is well known to produce its toxic effects by direct interference with cell metabolism through combination with sulphydryl groups (Stocken & Thompson 1949).

It is worth stressing these features because it has been suggested on a number of occasions that a Guillain-Barré type of illness may be an immunological response to a toxic agent. Such reports can be most difficult to substantiate or disprove and it is here that it is very easy to overstate the case against a chemical agent. It is to be hoped that better techniques for studying these problems will soon be developed.

Consideration of this difficulty leads to the important point that it may be possible to exclude neurotoxic effects. If these do not occur among a group of workers known to have been exposed to high concentrations of the substance in question then it is unlikely to be an important hazard under normal industrial conditions. For example, in a survey of 600 workers of the Rentokil Company, Morgan & Hickin (1966) found that absence through sickness was no higher than the national average. They also examined 14 workers in detail and found no evidence of toxicity. Although these important studies have shown that there is no danger in the normal use of Rentokil preparations, they do not tell us what may happen after accidental overexposure.

Table 2
Criteria for implicating an immunological mechanism in the production of neuropathy

Clinical features: abrupt onset, asymmetrical, other allergic manifestations
Unrelated to dose

Furthermore, it may be possible to say that a substance is unlikely to have been the cause of neuropathy in a particular patient if the clinical picture differs from that in known cases of poisoning. For example, it has occasionally been suggested that the chlorinated naphthalenes such as dieldrin and aldrin may produce peripheral neuropathy. But the characteristic features of poisoning by these substances are myoclonic jerks and fits, and workers with these symptoms have not developed neuropathy (Patel & Rao 1958).

In the case of pentachlorophenol, the situation is more difficult. The typical features of acute poisoning are well known and consist of an increase in metabolic rate with hyperpyrexia. Neuropathy is not part of the usual picture (Bergner *et al.* 1965). There is, however, an account of one man who developed various peripheral nerve palsies after gross overexposure of his arms to the liquid (Hernberb & Pessi 1964). In this instance, it seems possible that the effect might have been a local one following absorption through the skin.

As a result of high standards in industry today, most cases of clinical neuropathy are either a result of accidents or are due to substances new to industry. However, it is important to consider whether workers exposed to low levels of known toxic substances may develop minor degrees of peripheral nerve damage insufficient to cause any symptoms or signs. Lloyd Davies (1965) has discussed this problem in relation to other aspects of lead poisoning.

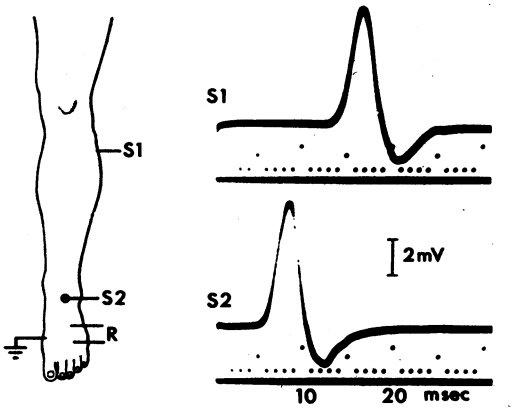

Fig 1 *Position of stimulating and recording electrodes and example of control muscle action potentials recorded from extensor digitorum brevis through surface electrodes. In each instance the stimulus occurs at the beginning of the sweep*

We have recently had the opportunity of trying to answer the question in relation to lead neuropathy and some preliminary findings are described below. This is part of a larger study being undertaken by Catton *et al.* (1969). Electrophysiological studies were carried out on the peripheral nerves of 5 men exposed to lead during their work. They all had raised blood lead levels with mild anæmia and one had had abdominal pain. They had no abnormal neurological symptoms or signs. Twelve age-matched control subjects were studied for comparison. Briefly, the electrophysiological techniques and findings were as follows. Muscle action potentials were recorded through surface electrodes over extensor digitorum brevis on the dorsum of the foot. The lateral popliteal nerve was stimulated at the head of the fibula and the anterior tibial nerve at the ankle (Fig 1). There was no abnormality of motor nerve conduction velocity between knee and ankle in the lead workers. The amplitude of the muscle action potential (height of the negative deflection above the base line) was measured following stimulation at the two sites. From Fig 2 it can be seen that there was no difference between the two groups. However, when the amplitude of the potential following stimulation at the knee was expressed as a percentage of that following stimulation at the ankle a difference emerged. The difference between the two means is significant at less than 0·01 level (Student 't' test). The most likely explanation of this observation is that conduction velocity was reduced in only a few fibres. This would not affect maximal velocity but the potential would become more dispersed the greater the conduction distance and thus affect the ratio. The method we have used is a very sensitive way of detecting minimal peripheral nerve damage.

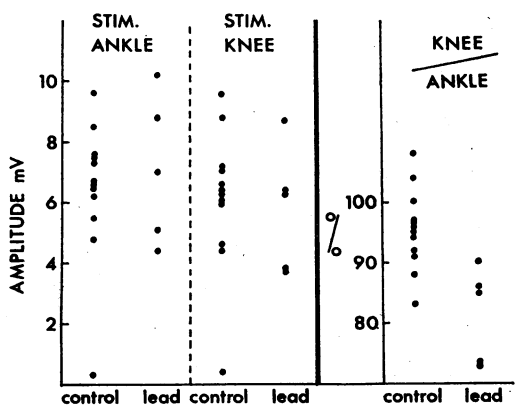

Fig 2 *Amplitude of the negative deflection of the muscle action potential recorded from extensor digitorum brevis in 12 control subjects and 5 lead workers*

These observations raise a familiar problem: What degree of exposure should one accept as tolerable? With increasingly refined methods of investigation it will no doubt be possible to detect damage produced by a number of substances, but which is not causing any clinical effect. We have to decide whether this matters and also what standards are possible in economic terms.

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