Toxic polyneuropathy of shoe-industry workers

A study of 122 cases

C. CIANCHETTI, G. ABBRITTI, G. PERTICONI, A. SIRACUSA, AND F. CURRADI

From Clinica delle Malattie Nervose e Mentali dell'Università di Cagliari, Istituto di Medicina del Lavoro dell'Università di Perugia, and Servizio di Neurofisiopatologia dell'Ospedale Generale Regionale di Perugia, Italy

SYNOPSIS The toxic polyneuropathy observed in a group of shoe-industry workers in Italy was clinically characterised by a symmetrical prevalently distal motor deficit, with occasional marked weakness of pelvic girdle muscles, and frequently by only subjective sensory symptoms; non-specific disturbances usually preceded neurological signs. Subclinical cases of 'minimal' chronic neuropathy, characterised by alterations of a neurogenic type in the EMG without a reduction of motor nerve conduction velocity, were also observed. Worsening of the clinical picture, with further lowering of nerve conduction velocity, was noted in some cases up to four months after removal from the toxic environment. In the most severe cases clinical recovery took up to three years. The electromyographic and electroneurographic features were consistent with a mixed, mainly axonal neuropathy, with clear prevalence of the damage in the distal part of the nerve (dying-back neuropathy). Volatile substances, such as n-hexane and other low boiling point hydrocarbons found in high percentage in solvents and glues, are suggested as the causative agent.

Widely distributed in many regions of Italy is an occupational toxic polyneuropathy which is commonest among workers in the shoe industry but also affects manufacturers of bags, suit-cases, and rain-coats. All of these processes involve the use of rubber-paste adhesives and organic solvents. This type of polyneuropathy closely resembles the n-hexane polyneuropathy described among manufacturers of sandals in Japan (Sobue *et al.*, 1968; Yamamura, 1969) and in workers in other occupations (Yamada, 1964, 1967; Herskowitz *et al.*, 1971), and in glue-sniffers (Matsumura *et al.*, 1972; Takenaka *et al.*, 1972; Goto *et al.*, 1974; Shirabe *et al.*, 1974; Korobkin *et al.*, 1975; Towfighi *et al.*, 1976). The purpose of this paper is to report clinical, electromyographical, and laboratory findings in 122 subjects affected by this toxic polyneuropathy. The aetiology is more extensively discussed in another paper (Abbritti *et al.*, 1976).

METHODS

One hundred and twenty-two workers in the shoe industry, 83 females and 39 males, aged 15 to 59 years (mean 35 years), were admitted to our hospital in

Perugia during the period 1971-74, from the regions of Marche (106 cases), Umbria (eight cases), and Tuscany (eight cases). Most patients showed clear-cut signs of neuropathy, but some had only subjective complaints and were sent to the hospital for a more accurate examination.

Each patient was submitted to the following investigations: (1) full neurological and general examination; (2) coaxial needle electromyography (EMG) and motor nerve conduction velocity (MCV); the latter was measured in every patient in the peroneal and ulnar nerves, using standard techniques; lower normal values of the MCV in our laboratory for peroneal nerve (from knee to ankle) are 45 m/s (mean 51.4 m/s, SD 4.1) and for ulnar nerve (from elbow to wrist) are 47 m/s (mean 56.3 m/s, SD 5.2); femoral nerve conduction time from the ligamentum inguinale to the vastus medialis muscle was also measured in every patient; (3) complete blood cell count; erythrocyte sedimentation rate; liver function tests; blood urea nitrogen; blood glucose; urinalysis.

Cerebrospinal fluid was examined in the most severe cases (seven patients), in three of whom the nature of the onset and the clinical picture initially suggested the possibility of an acute polyradiculoneuritis. Twenty patients were given EEG and 12 patients were given cochleovestibular tests. Plasma

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cholinesterase activity was measured in 58 cases. Unfortunately, it was not possible to perform nerve biopsy. Diagnosis of neuropathy was based on reduction of nerve conduction velocity and/or neurogenic signs on electromyography. Diagnosis of occupational disease was suggested by the fact that all patients worked in the same industry or in industries where similar kinds of work were carried out. Moreover, diagnosis was confirmed by the absence of clinical and anamnestic evidence for (1) other diseases able to cause peripheral nerve pathology, and (2) exposure to toxic substances outside the work environment. Patients with confirmed or even suspected chronic alcoholism, diabetes, liver or kidney diseases were excluded from this study.

The interval of time that elapsed between the appearance of subjective complaints, and of exposure to the toxic environment, and the results of the first EMG and clinical examination were noted. In 53 patients out of 79 with reduced nerve conduction velocity (groups I and II; *vide infra*), clinical and EMG examinations were repeated every three to six months, until MCV became normal. Other patients are still under periodic examination. Twenty-nine patients out of 43 of group III, without decrease of nerve conduction velocity, were studied until one year after stopping work; during the period of observation they did not attend their place of work.

A control group of 17 subjects who showed neither objective nor electromyographic signs of neuropathy, but who worked in the same industries and complained of subjective symptoms similar to those reported by the patients with signs of neuropathy, was also studied.

Tasks performed in the shoe industry by our patients were divided into three types: (1) gluing, which involved contact with rubber-paste adhesives; (2) cleaning, which involved the use of solvents of glues; (3) all other functions (more than 10), which did not involve direct contact with glues or solvents.

Exposure was distinguished as 'generic' (the number of years of work in the shoe industry whatever the task), and 'specific' (the number of years of work at the task during which the first symptoms of the disease appeared).

RESULTS

Since the reduction in motor nerve conduction velocity was greatest in the peroneal nerve in all patients, they were classified into three groups on the basis of the conduction velocity of the fastest motor fibres of the peroneal nerve.

Group I Thirty-seven patients with motor nerve conduction velocity less than 35 m/s.

Group II Forty-two patients with motor nerve conduction velocity between 35 and 44 m/s.

Group III Forty-three patients with normal conduction velocity, but with neurogenic alterations in the EMG.

Many patients were examined several times and some deteriorated after the first examination (see below); therefore the above classification is based on the lowest conduction velocity value recorded. However, we cannot affirm that all patients were examined in their worst phase (although this surely occurred in the most severe cases), as some came to us several months after the onset of symptoms and/or stopping work.

The mean values of the intervals between the appearance of subjective symptoms and the end of exposure are: 30.9 days (range four to 120) for group I, 48.2 days (range five to 150) for group II, 354.3 days (range seven to 730) for group III. Mean values of the intervals between the end of the exposure and the date of the first EMG and clinical examination are: 37.7 days (range two to 110) for group I, 42.2 days (range two to 160) for group II, 32.7 days (range three to 180) for group III.

On average, the interval between appearance of subjective symptoms and stopping exposure increases from group I (more severe cases and acute or subacute course), to group III (fewer disturbances, very slow course). The average interval between stopping work and the first EMG was similar but with considerable variation between the three groups, as some patients were referred to us after being in other hospitals.

CLINICAL FEATURES

In patients in groups I and II, the disease frequently assumed a subacute course, but the most severe cases showed a fully developed clinical picture within a few weeks. General symptoms, such as anorexia, weight loss, nausea, vomiting, headache, epigastric pain, constipation, dizziness, and insomnia frequently preceded or accompanied symptoms of the neuropathy. They preceded it in 27 (73%) cases of group I, and in 33 (78.5%) cases of group II. The clinical symptoms related to the neuropathy were subjective (weakness, paraesthesias, and cramp-like muscular pain) and objective (motor impairment, changes in muscular tone, trophism and tendon reflexes, hypoaesthesia); these symptoms affected, as a rule, the distal part of the limbs, symmetrically. Most patients in group III suffered for a long period from subjective symptoms (both general and related to neuropathy) which did not assume a clearly progressive course but remained almost unchanged for months or even years; several patients of this group stopped working and came to

the hospital only after some of their colleagues were found to be affected by polyneuropathy.

Subjective complaints were also present, as mentioned above, in the control group of shoe-industry workers. Table 1 illustrates the incidence of the general symptoms in the different groups. These were not clearly related to the severity of the neuropathy, with the exception of anorexia and weight loss which had a higher incidence in more severely affected patients. The incidence of the subjective symptoms related to neuropathy is shown in Table 2; weakness and paraesthesias appeared proportional to the severity of the neuropathy, whereas cramp-like pain did not.

Objective signs (Tables 3 and 4) concerned essentially groups I and II, as group III is represented by subjects with little or no clinical impairment. Motor impairment dominated the clinical picture in groups I and II. In most cases, weakness, hypotonia, muscle-wasting, and reduction of tendon reflexes were most evident in the lower limbs and distally. In some patients, however, an important proximal involvement (pelvic girdle and thigh, mainly in the territory of distribution of the femoral nerve) was also found: a pseudomyopathic gait was observed in such cases (five of group I and two of group II). Facial muscles

were involved only in very severe cases. Some patients of group I became almost completely paralysed. At a late stage of evolution, we observed mild hyperreflexia in some patients of group I and II; mild hyperreflexia was also frequently observed in group III patients from the first examination. However, we never noted Babinski's sign.

Objective sensory signs were of a mild degree and distally localised, and they usually involved only superficial sensations. Trophic vasomotor disturbances of the skin were present distally in the most severe cases. The probable neuropathic origin of dizziness was suggested by the finding of slight modifications of vestibular tests in two patients of group I, and in two of group II. We never noted anosmia, optic disc atrophy, visual disturbances, auditory changes, cerebellar signs, or sphincter disturbances.

ELECTROMYOGRAPHY AND NERVE CONDUCTION VELOCITY

Mean, standard deviation, and range of motor nerve conduction velocities observed in peroneal and ulnar nerve of groups I and II patients are shown in Table 5. For each nerve, both the values found at the first

TABLE 1
GENERAL SYMPTOMS

Group	Cases (no.)	Anorexia and weight loss		Nausea or vomiting		Epigastric pain		Headache		Dizziness		Insomnia	
		no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
I	37	22	59.4	12	32.4	11	29.7	12	32.4	9	24.3	5	13.5
II	42	24	57.1	11	26.2	10	23.8	20	47.6	12	28.6	6	14.3
III	43	9	20.9	10	23.2	13	30.2	19	44.2	6	13.9	5	11.6
Controls	17	3	17.6	2	11.8	5	29.4	7	41.2	7	41.2	6	35.3

TABLE 2
SUBJECTIVE SYMPTOMATOLOGY AT UPPER AND LOWER LIMBS

Group	Cases (no.)	Weakness				Paraesthesias				Cramp-like pain			
		Upper		Lower		Upper		Lower		Upper		Lower	
		no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
I	37	27	72.9	37	100	29	78.4	35	94.5	10	27.0	22	59.4
II	42	33	78.5	39	92.8	31	73.8	37	88.2	14	33.3	36	85.7
III	43	16	37.2	22	51.2	14	32.5	36	83.8	12	27.9	29	67.4
Controls	17	8	47.0	16	94.1	4	23.5	9	52.9	2	11.7	13	76.5

TABLE 3
OBJECTIVE SYMPTOMS

	<i>Muscle hypotonia</i>		<i>Muscle wasting</i>		<i>Hypoaesthesia</i>	
	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>
Group I (37 cases)	23	62.2	18	48.6	13	35.1
Group II (42 cases)	8	19.0	5	11.9	7	16.7
Group III (43 cases)	0		0		3	6.9

examination and the minimal value measured in each patient during the course of the disease are given. Greatest lowering of motor conduction velocity was observed in the peroneal nerve. The femoral nerve was also markedly affected in some cases: conduction time from the inguinal ligament to the vastus medialis was longer than 10 ms in seven cases of group I and in one case of group II.

Of interest was the progressive fall in the conduction velocity observed in some patients (nine of group I, and five of group II) even after removal from

their work environment (Fig. 1); this occurred after at least four months in one case; clinical deficit also increased in the same period. As can be seen in Fig. 1, we never observed very low values of MCV, either before or after the period of a non-evocable muscle response (MAP). In the amelioration phase, sometimes the MAP was evocable for a certain period only by stimulation of the proximal part of the nerve (Fig. 1, d.n.e. = MAP not evocable at the ankle). The distal latency was as a rule strikingly prolonged. Deterioration of MCV was not found to be correlated with age, body weight, length of exposure, or task performed in the shoe-industry. The phenomenon is probably more diffuse, because, as already mentioned (Table 1), many subjects came to us late.

The amplitude of the MAP was always clearly reduced in patients of groups I and II (group I, extensor digitorum brevis: mean 1.7 mV), but rarely in patients of group III. Other electroneurographic data are not available for all the patients. At the first control in groups I and II, the distal latency (DL) for peroneal nerve to extensor digitorum brevis muscle was more than 7 ms in nine of the 23 cases examined (40%) and the duration of the MAP evoked at the stimulation of the nerve at ankle was longer than

TABLE 4
TENDON REFLEXES

	<i>Achilles</i>				<i>Quadriceps</i>				<i>Cubital and radial</i>				<i>Triceps and biceps</i>			
	<i>Reduced</i>		<i>Absence</i>		<i>Reduced</i>		<i>Absence</i>		<i>Reduced</i>		<i>Absence</i>		<i>Reduced</i>		<i>Absence</i>	
	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>	<i>no.</i>	<i>%</i>
Group I (37 cases)	13	35.1	23	62.2	17	45.9	18	48.6	18	48.6	8	21.6	17	45.9	7	18.9
Group II (42 cases)	12	28.6	15	35.7	15	35.7	12	28.6	19	45.2	3	7.1	21	50.0	1	2.4
Group III (43 cases)	7	16.3	2	4.6	13	30.2	0		5	11.6	0		5	11.6	0	

TABLE 5
VALUES OF MOTOR NERVE CONDUCTION VELOCITY (M/S) IN GROUPS I AND II*

<i>Values</i>	<i>Group I</i>			<i>Group II</i>		
	<i>Mean</i>	± 1 <i>SD</i>	<i>Range</i>	<i>Mean</i>	± 1 <i>SD</i>	<i>Range</i>
Peroneal nerve MCV						
At 1st exam.	30.1	4.0	0-34.5	38.4	2.9	35-44
Minimal	24.8	11.9	0-34.5	38.1	2.9	35-44
Ulnar nerve MCV						
At 1st exam.	41.8	5.7	30-53	46.7	4.6	38-57
Minimal	39.1	10.8	0-53	46.5	4.5	38-57

*In the calculation of the means, the absence of a motor response at nerve stimulation is given as zero m/s of MCV.

FIG. 1 Evolution of motor nerve conduction velocity in 14 subjects in whom it continued to worsen even after removal from the work environment (the removal is taken as zero time); nm = not measurable; dne = distally not evocable—that is, MAP not evocable by stimulation of peroneal nerve at ankle.

14 ms in seven of 29 cases (24%). In successive controls, before the normalisation of the maximal MCV, DL was lengthened in a higher percentage of patients and the duration of the MAP at the ankle stimulation was lengthened in 100% of the patients examined. A typical case in this stage of evolution is presented in Fig. 2. At the first normal value of MCV, the DL was still abnormal in 20.7% cases and MAP duration in 51.9% of cases. In patients of group III, MAP duration was increased in 52% of cases, while distal latency was increased in only one patient.

Electromyographic examination in patients of group I and II always showed signs of loss of motor units (reduced interference pattern, roughly proportional to the degree of clinical motor impairment) with modification of their structure and signs of slowing of conduction in terminal nerve fibres (increase of polyphasic and irregular potentials) and spontaneous activity of denervated fibres (mainly fibrillation).

In group III, there was a loss of motor units, although usually slight, as well as motor unit changes; fibrillation activity was detected in about half of the cases; the mean dispersion of motor unit action potential duration was increased in spite of the normal values of maximal and minimal MCV in the leg. This pattern was found mainly in distal muscles.

Electromyography and conduction velocity in the control group were completely normal.

LABORATORY FINDINGS

Plasma cholinesterase levels are reported in Table 6. The slight changes noted, with respect to the standard values given by the laboratory, were also observed in a supplementary control group of 10 subjects (neurotic, not shoe workers), and were not statistically significant. There is, therefore, no evidence of involvement of this enzyme.

FIG. 2 Group I patient eight months after stopping work. Peroneal nerve, extensor digitorum brevis muscle. Stimulation at head of the fibula and at ankle. MCV: 31 m/s; distal latency increased; MAP duration highly prolonged but superimposable at the two levels of stimulation.

Slight hypochromic sideropenic anaemia (haemoglobin between 9.8 and 11.5 g/dl) was found in some patients, all females: four of group I (10.8%), one of group II (2.4%), four of group III (9.3%), and one of the control group (6%). In all cases anaemia disappeared with iron therapy.

Blood platelets were slightly less than $140 \times 10^3 \text{ mm}^{-3}$ in three patients of group I (8.1%), three of group II (7%), four of group III (9.3%).

No abnormalities were found in blood glucose, blood urea, nitrogen, urinalysis, erythrocyte sedimentation rate, or liver function tests.

CEREBROSPINAL FLUID

The CSF examination in seven patients showed no abnormalities.

ELECTROENCEPHALOGRAM

In the 20 patients examined (six of group I; eight of group II, six of group III), no marked changes were

TABLE 6
PLASMA CHOLINESTERASE LEVELS (mU/ml)

	Mean	$\pm 1 \text{ SD}$
Group I (15 cases)	2.050	0.621
Group II (21 cases)	2.499	0.618
Group III (22 cases)	2.573	0.954
Control group A (shoe workers, 12 cases)	2.272	0.626
Control group B (not shoe workers, 10 cases)	2.445	0.610

t test: (1) Control A vs. group I, vs. group II, vs. group III $p = \text{NS}$.
(2) Control B vs. group I, vs. group II, vs. group III $p = \text{NS}$.

noted except in two patients of group I and one of group II, where theta rhythms and/or sharp waves were present bilaterally.

EVOLUTION

The nerve conduction velocity measurement was employed as the main parameter to evaluate the course of the disease. Patients of group I and II, after stopping work, usually improved slowly, although a deterioration was noted in some (Fig. 1). The time for conduction velocity to return to normal in 51 subjects (21 of group I, and 30 of group II), is shown in Table 7; in the most severe cases this was 30 months from the time of stopping work. Three patients of group I still have a decreased motor nerve conduction velocity after 2½ years. Subjective complaints such as cramp-like pain, weakness, and fatigue often continued even when conduction velocity had become normal; atrophy was observed in the more affected muscles in the most severe cases. Tendon hyperreflexia was also found in several cases. As mentioned above, at the time of the first normal value of MCV, the distal latency was often found to be still high. The

TABLE 7

TIME REQUIRED FOR MAXIMAL MOTOR NERVE CONDUCTION VELOCITY OF PERONEAL NERVE TO RETURN TO NORMAL

	Months							
	3	6	9	12	15	18	24	30
Group I (21)	—	1	2	4	3	7	2	2
Group II (30)	3	8	3	10	4	2	—	—

Calculated in months from the last day of exposure.

electromyographic findings were those usually observed after different degrees of denervation with signs of reinnervation (reduced interference pattern with increased polyphasic potentials).

In group III patients, subjective complaints improved after a period away from work, but in several cases had not disappeared after one year of observation. The EMG showed little or no variations during the same period, thus confirming the chronic character of the lesion.

FUNCTION AND DURATION OF EXPOSURE

Table 8 shows the relationship between functions performed by workers at the time of onset of polyneuropathy and the severity of the disease. It is evident that polyneuropathy can occur in its different forms irrespective of the task performed, and of direct contact with glues and/or solvents. Taken as a whole, the results show that the single tasks which carry the major risk of polyneuropathy are gluing and cleaning the finished goods with solvents; 71.3% of the patients performed these two tasks in which only 20–25% of the workers are usually engaged, whereas the remaining 28.7% of the patients were engaged in more than one of the 10 other tasks carried out in the shoe industry. Data on exposure are shown in Table 9.

TABLE 8
TASKS

	Gluing	Cleaning	Other tasks
Group I (37 cases)	15 (40.5%)	6 (16.2%)	16 (43.2%)
Group II (42 cases)	19 (45.2%)	19 (45.2%)	4 (9.5%)
Group III (43 cases)	22 (51.2%)	6 (13.9%)	15 (34.9%)
Controls (17 cases)	14 (82.4%)	1 (5.9%)	2 (11.8%)

TABLE 9
LENGTH OF EXPOSURE (YEARS)

Subjects (no.)	Generic		Specific	
	Mean	Range	Mean	Range
Group I (37 subjects)	5.4	0.1–9	3.0	0.1–9
Group II (42 subjects)	6.8	0.1–22	4.1	0.1–10
Group III (43 subjects)	11.7	0.7–31	7.3	0.3–23
Controls (17 subjects)	11.0	0.2–26	8.8	0.2–26

t test either for generic or specific exposure: I vs. II: $P = \text{NS}$, III vs. controls: $P = \text{NS}$, I vs. III: $P < 0.01$, I vs. controls: $P < 0.01$, II vs. III: $P < 0.01$, II vs. controls: $P < 0.01$.

Longer exposure, either generic or specific, is exhibited by group III patients ($P < 0.1$), according to the extremely chronic evolution and slight relevance of their neuropathy, and by controls. The disease was observed in some cases of group I and II after only one month of exposure.

DISCUSSION

In our cases, polyneuropathy of shoe-industry workers was characterised by the following features: occurrence in subjects exposed to volatile solvents (minimal exposure: about one month); slow onset (acute only in some of the most severe cases) usually after general prodromal symptoms (anorexia, weight loss, nausea, headache, epigastric pain, etc); symmetrical picture with prevalent motor impairment of the distal part of the lower limbs but occasionally also of thigh and pelvic girdle; mainly subjective sensory disturbances; usual absence of involvement of cranial nerves; possibility of further worsening for a few months after withdrawal from exposure; and finally presence of a 'minor' form of the disease with almost exclusively subjective symptomatology, chronic course, and electromyographic alterations. Type of work, solvents used and clinical picture are similar to those of the *n*-hexane neuropathy described in Japan by Sobue *et al.* (1968) and Yamamura (1969); also similar, except for the work performed, are the cases of Yamada (1964, 1967) (polyethylene and pharmaceutical industries), of Herskowitz *et al.* (1971) (cabinet finishers) and of Goto *et al.* (1974), Shirabe *et al.* (1974), Korobkin *et al.* (1975), Towfighi *et al.* (1976) (glue sniffers). However, in the cases reported by Yamamura (1969), objective sensory disturbances appeared to be more frequent and severe, and in some patients involvement of cranial nerves I and II was noted, while general symptoms and muscle wasting were much less frequent and pelvic girdle involvement is not described. The latter was, on the contrary, much more evident in five cases of neuropathy in shoe-industry workers described some years ago by us (Borri *et al.*, 1967), and in several patients of Cosi *et al.* (1973). No subjective general symptoms are reported in the case of glue-sniffing neuropathy, while subjective sensory disturbances appear almost to be constant (Goto *et al.*, 1974; Shirabe *et al.*, 1974; Korobkin *et al.*, 1975).

In our study, the electromyographic and electro-neurographic features are indicative of a mixed although prevalently axonal lesion. The occurrence of demyelinating processes is evident in the more severe degrees of the lesion (groups I and II) where a reduction of MCV higher than 40% of normal mean values is present (Gilliat, 1966), besides the signs of denervation and of reduction of activable motor units, due to

axonal lesion. Moreover, other data suggest the prevalence of the lesion in the distal part of the nerve: in fact the frequent increase of the distal latency and of the duration of the MAP, which in some cases occurred also when MCV was normal, indicates a delayed conduction in the distal part of the nerve in absence of damage in the more proximal part. This is comparable with the observation of Fullerton (1969) in acrylamide neuropathy and suggests a similar pathological process (dying-back neuropathy). The electrophysiological reports of Iida *et al.* (1969) on shoe-workers in Japan are in many respects not dissimilar to our findings, although these authors draw different conclusions, probably because of lack of data on the distal conduction.

The comparison of our electrophysiological pattern with the reports of nerve biopsies by other authors in neuropathies probably due to the same or strictly similar agents, is not easy. The findings of Herskowitz *et al.* (1971), Goto *et al.* (1974), Shirabe *et al.* (1974), Korobkin *et al.* (1975), and Towfighi *et al.* (1976) are those of a prevalent axonal (mainly paranodal) swelling due to accumulation of neurofilaments, and scattered demyelination assumed to be secondary. This pattern is also typical of neuropathies due to other chemically akin substances such as methyl-n-butylketone (Allen *et al.*, 1975; Spencer *et al.*, 1975) and 2,5-hexanedione (Spencer and Schaumburg, 1975). Similar findings, however, are observed in acrylamide (Prineas, 1969b; Schaumburg *et al.*, 1974) and TOCP (Prineas, 1969a) neuropathies, which are considered to be typical dying-back neuropathies (Cavanagh, 1964; Fullerton and Barnes, 1966). This substantiates our interpretation on the electrophysiological basis, although we lack biopsy findings.

Apart from the picture of the clinically evident cases of groups I and II, that of group III merits further consideration. The group was delineated by a systematic electromyographic and electroneurographic examination of patients with little or no objective signs. The more frequent electrophysiological aspects, especially in those patients complaining of long-continued disturbance, are consistent with a 'minimal' chronic neuropathy due to axonal damage limited to a few fibres, so that in time denervation is largely compensated for by regeneration or by collateral branching of healthy fibres. The possibility of a regenerative process occurring while toxic exposure continues was demonstrated in acrylamide poisoning by Fullerton and Barnes (1966) and in other toxic neuropathies (Spencer and Schaumburg, 1975; Spencer *et al.*, 1975). The electroneurographic demonstration of the worsening of the neuropathy in some patients of groups I and II for a few months after leaving work is of interest and as yet unexplained. This was also noted clinically by Yamamura (1969), Goto

et al. (1974), Shirabe *et al.* (1974), and Korobkin *et al.* (1975) in n-hexane neuropathy and in neuropathies due to TOCP (Becker, 1961; Gross, 1967), thalidomide (Simpson, 1963; Hafström, 1967) and methyl-n-butylketone (Allen *et al.*, 1975). A hypothesis that could explain this type of evolution is that of a prolonged storage of the toxic agent in the body and an irreversible damage to important structures for motoneuronal metabolism.

Differences in amounts of toxic substances absorbed by workers as a consequence of the variable extent of environmental pollution may explain why the disease sometimes occurs in a form so mild as to permit normal, or almost normal work for months (patients of group III), while at other times it begins and evolves so rapidly as to cause complete paralysis within one to two months. Our data on evolution of the disease cast some doubt on the prospect of a full recovery without residual symptoms which has been claimed by the authors who have studied cases from shoe-industries in other regions of Italy. Subjective complaints and muscle atrophy in the most severe cases often continued after normalisation of MCV. The frequently noted tardive tendon hyperreflexia, although not disturbing to the patient, should also be considered a residual symptom; this was particularly marked, with clonic and sphincter disturbances, in a case reported by Faggi *et al.* (1971), which, however, had a favourable outcome within six months. Mild pyramidal tract involvement may be the cause (even if the Babinski sign was never reported), and this could indicate a central action of the neurotoxic agent.

For the evaluation of any possible central neurotoxic effect, EEG is an additional tool; in this respect, our generally normal data differ from that of Faggi *et al.* (1972) who found alterations in 23 out of 31 subjects.

In polyneuropathies of shoe-workers, cholinesterase levels were found to be depressed in 26 cases out of 42 by Yamamura (1969), and in erythrocytes, but not in plasma, by Faggi *et al.* (1971), while Crepet *et al.* (1968) found it always normal in erythrocytes, as well as in plasma. Our study of plasma cholinesterase levels showed no significant variation between exposed workers and the control group. This contrasts with the hypothesis of an aetiological importance of triorthocresylphosphate (TOCP) which has been shown to cause inhibition of plasma cholinesterase (Hunter, 1975).

No definite involvement of the haematopoietic system has been found apart from a mild decrease in platelet counts in some patients: this might be due to small amounts of benzene occasionally present in glues and solvents, or to the action of the other organic solvents largely used in the shoe industry.

As far as aetiology is concerned, the toxic agent previously considered by many Italian authors (Isotti and Saraval, 1958; Crepet *et al.*, 1968; Cosi *et al.*, 1973; Fasanaro, 1973) to be responsible for neuropathy in Italian shoe-industry workers is triorthocresylphosphate (TOCP), a non-volatile substance contained or suspected to be contained in glues, which may be absorbed through the skin and gastrointestinal tract. Indeed, the clinical, electromyographic, and histological picture (as above mentioned) may have aspects similar to those of the TOCP neuropathy (Herskowitz *et al.*, 1971; Shirabe *et al.*, 1974). However, TOCP has never been demonstrated in appreciable quantity in the materials analysed by other Italian authors (Capellini *et al.*, 1968; Crepet *et al.*, 1968) and by us.

Two main facts support the hypothesis that the agent responsible is a volatile substance (Abbritti *et al.*, 1976): first, the evidence that the polyneuropathy affects not only workers engaged in gluing, but also workers involved in cleaning finished shoes with organic solvents and even those who have no direct contact either with glues or solvents although working in the same environment (Table 8); second, the fact that the disease sometimes manifests itself in epidemic form, especially during the winter, in small factories where standards of hygiene are very poor, whereas in larger industries with better environmental and personal hygiene, only the mildest form of the disease is found.

Samples of solvents and glues collected by us in five different factories (with a total of 20 workers affected by the disease) gave evidence for the constant presence in very high concentrations (from 79 to 98% of the solvent by volume) of paraffinic hydrocarbons of a low boiling point (pentane, isopentane, 2-methylpentane, 3-methylpentane, n-hexane, heptane, isohexane) (Abbritti *et al.*, 1976).

In materials used in sandal factories in Japan, where cases of polyneuropathy occurred, Inoue *et al.* (1970) found a similar composition. The experimental demonstration of the neurotoxic activity of similar mixtures (described commercially as 'n-hexane', referring to the main component) was given by Miyagaki (1967), Kurita (1967) and Truhaut *et al.* (1973). The pure n-hexane was, on the contrary, found experimentally unable to cause neuropathy also in high concentration during several months (Foà *et al.*, 1976).

Toluene, found in considerable amounts (24 to 55%) in materials inhaled in cases of glue-sniffers' neuropathy (Goto *et al.*, 1974; Shirabe *et al.*, 1974; Korobkin *et al.*, 1975) was lower than 2% in our solvents.

Methyl-n-butyl-ketone, an experimentally demonstrated neurotoxic substance (Duckett *et al.*, 1974;

Mendell *et al.*, 1974; Spencer *et al.*, 1975), causative agent of several cases of neuropathy in an industry producing plastic-coated and colour-printed fabrics (Allen *et al.*, 1975), was completely absent in our materials, as well as methyl-ethyl-ketone. However, the many similarities among these toxic neuropathies raise the possibility of a similar metabolic mechanism.

Additional experimental studies are required to establish if the effects on the nervous system are due to only one of these substances or to a synergistic action of two or more of them; the latter hypothesis seems to us more probable.

It is possible that variations in the clinical picture noted by different authors with regard to the general disturbances, cranial nerve and pelvic girdle involvement, pyramidal tract damage, EEG picture, plasma cholinesterase levels, blood platelet number, evolution, etc., may reflect the presence of a different percentage of the above-mentioned substances, or the occasional presence of other neurotoxic solvents.

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