Shoe-makers' polyneuropathy in Italy: the aetiological problem

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Abbritti, G., Siracusa, A., Cianchetti, C., Coli, C. A., Curradi, F., Perticoni, G. F., and De Rosa, F. (1976). *British Journal of Industrial Medicine*, 33, 92-99. **Shoe-makers' polyneuropathy in Italy: the aetiological problem.** Since 1957, when the first cases of the so-called shoe-makers' toxic polyneuropathy were reported, nearly 400 cases have been described in the Italian literature. The substance that was considered to be responsible for the disease was triorthocresylphosphate (TOCP) contained in glues, artificial leathers, and some types of paints. However numerous chemical analyses of glues and leathers taken from factories where cases of the disease occurred have shown that in almost all instances little or no TOCP was present. In addition the disease manifests itself more frequently during winter and spring and this is not consistent with the absorption of the causative agent through the skin and/or gastrointestinal tract. In order to clarify the aetiology of the disease 122 workers in the shoe industry affected by toxic polyneuropathy during the period 1971-74 were studied. Work-places where cases of polyneuropathy had occurred were visited and samples of glues and solvents were taken for chemical analysis. The polyneuropathy chiefly affects workers engaged in glueing and in the cleaning process, but it also affects those who do not have direct contact with glues or solvents. The disease is more common in women (68%) than in men (32%) and, in its more severe form, begins with overwhelming prevalence during winter and early spring regardless of the job performed. No direct relationship has been found between the severity of the disease and the number of years of work in the shoe industry or of specific exposure (that is the number of years of work in the activity performed at the onset of the disease). The polyneuropathy is found almost exclusively among workers of the artisan type in small shoe factories, where standards of hygiene are low. Chemical analysis of glues and cleaning fluids collected from five different factories, where 20 cases of polyneuropathy occurred, showed the presence of paraffin hydrocarbons with a low boiling point (pentane, 2-methyl-pentane, 3-methyl-pentane, n-hexane, etc.) in concentrations of more than 80% by weight.

Since 1957, when the first nine cases of polyneuropathy were reported among workers in different shoe factories (Isotti and Saraval, 1957), nearly 400 cases have been reported on in Italy. Table 1 shows the cases described during the period 1957-73. From an analysis of this table it is evident that the

frequency of the disease is steadily increasing. The year 1968 seemed to be the worst but this was probably because the Italian Congress of Occupational Health allocated one session to the study of the disease, so that many cases were reported on that occasion. The polyneuropathy affects mainly, although not exclusively, workers in the shoe and leather industry. The disease manifests itself most

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TABLE 1
SHOE-MAKERS' POLYNEUROPATHY IN ITALY

Reported cases from 1957 to 1973					
Authors	Year of publication	Total no. cases	No. cases in shoe and leather industry	Season of maximum frequency	Causative substance suspected
Isotti and Saraval	1957	9	9	?	?
Isotti and Saraval	1958	19	?	?	TOCP
Gatti and Saraval	1960				?
Fabiani and Bedogni	1962				?
Pretolani and Scotti	1963	13	13	Winter-Spring	TOCP
Mazzella di Bosco	1964	8	8	Winter-Spring	TOCP
Pinelli and Tonali	1964	1	1	Spring	TOCP
Gherardi	1965	15	15	Winter	TOCP
Del Greco and Cecchini ..	1966	8	8	Winter-Spring	?
Borri <i>et al.</i>	1967	5	5	Winter-Spring	TOCP + Solvents
Leoni	1967	6	5	Winter-Spring	?
Crepet <i>et al.</i>	1968	49	48	?	TOCP
Cappellini <i>et al.</i>	1968	47	25	Winter-Spring	TOCP
Maugeri and Candura	1968	11	11	?	TOCP
Ambrosetto	1968	10	10	?	TOCP
Ruggerini and Teso	1968	30	0	Winter-Spring	TOCP
Marroni	1968a	5	5	Winter-Spring	TOCP
Marroni	1968b	1	0	?	TOCP
D'Errico <i>et al.</i>	1968	7	7	Winter-Spring	TOCP
Graev <i>et al.</i>	1971	8	7	Winter-Spring	TOCP
Faggi <i>et al.</i>	1971	14	14	?	TOCP
Carnevale <i>et al.</i>	1973	2	2	Winter-Spring	Solvents (Hexane)
Montanari	1976	72	72	Winter-Spring	?
Battistini <i>et al.</i>	1973	6	6	?	?
Barone <i>et al.</i>	1973	50	50	Winter-Spring	TOCP

? Not reported or unknown

frequently during winter and spring, and the substance considered responsible for the disease was triorthocresylphosphate (TOCP), which is contained in glues, artificial leathers, and some types of paints.

The hypothesis that TOCP is involved in the aetiology has been supported as follows (Cappellini, Chiappino, and Zurlo, 1968):

Triorthocresylphosphate is used in the production of polyvinyl chloride plastics, paints, glues, and artificial leathers and is sometimes added to old stocks of glue to reactivate them; the clinical picture and the histopathological changes found among workers affected by this disease were similar to those found in patients with polyneuropathy due to exposure to TOCP which was not related to occupation, and to those found in experimental animals given TOCP; other known neurotoxic substances in the working environment that could have caused the disease were not found.

From a retrospective analysis of the reports there are several elements which in our opinion cast doubt on the importance of TOCP as the only or principal cause of the disease.

Numerous chemical analyses of the glues and leathers taken from factories where cases of the disease were found have shown that in almost all instances, little or no TOCP was present (Crepet *et al.*, 1968; Cappellini *et al.*, 1968). Moreover the disease manifests itself more frequently during winter and spring, and this is not consistent with the hypothesis of absorption of the causal agent through the skin and/or gastrointestinal tract.

In order to clarify the aetiology of the disease we studied 122 shoe industry workers affected by polyneuropathy during the period 1971-74.

This paper concerns the relationship between occupation and the frequency and severity of the polyneuropathy, between the severity of the disease and the age, sex, and length of exposure; and the relationship between the time of year and the onset and severity of the disease. The composition of glues and solvents used in different shoe factories in which there were 20 cases of polyneuropathy is also reported, together with some observations concerning these work places. The clinical and electromyographic details are given in another paper (Cianchetti *et al.*, in preparation).

Methods

Detailed information about the work place, the type of material used, the job performed at the onset of the disease and in previous years and a detailed description of the symptoms, their order of appearance and evolution was obtained from every worker affected by polyneuropathy.

All patients were given an electromyographic examination in addition to laboratory investigations necessary to exclude the presence of other diseases that could cause polyneuropathy, such as diabetes, chronic alcoholism, etc. In none of the cases observed was there evidence of any past contact with chemicals such as lead, arsenic, carbon disulphide, etc. or drugs such as sulphonamides, deemed capable of causing polyneuropathy.

When patients came under observation within a few days after stopping work, we visited their work places and took samples of glues and solvents used for chemical analysis.

The patients were divided into three groups according to the severity of the polyneuropathy, using as the reference parameter the maximum motor conduction velocity (MCV/max) of the peroneal nerve (PN):

Group I: with MCV/max of PN less than 35 m/s;
Group II: with MCV/max of PN between 35 and 44 m/s;
Group III: with MCV/max of PN equal or greater than 45 m/s, but with clear electromyographic signs of neurogenic alteration (reduced interference pattern; increase of polyphasic and irregular potentials; increase of voltage and duration; spontaneous activity of denervated fibres).

The peroneal nerve was chosen as the reference parameter because it was almost always shown to be the nerve with maximum proportional reduction of MCV values. The patients we examined came from 72 shoe factories in different provinces and regions of Italy (Table 2) and this suggests that the disease is caused by substances in widespread use.

Results

Table 3 shows the relationship between occupation and the frequency and severity of polyneuropathy. The jobs which carried the major risk were glueing and cleaning of the finished goods with solvents. In fact 71.3% of the patients performed these two

jobs in which usually only 20-25% of workers are engaged, whereas the remaining 28.7% of the patients worked in more than 10 other jobs into which the productive cycle of the shoe industry is divided. It is also worth noting that the patients in the last group had no direct contact with glues and solvents.

In Table 4 the relationship between the severity of the disease and age, sex, and specific and total length of exposure is analysed. The age of patients ranged from 15 to 59 years with an average of 34.8 years. No significant age differences exist between the three groups. The disease was most frequently found among women (68%) probably because they are mainly engaged in duties which carry the major risk (glueing and cleaning). No direct relationship existed between the severity of the disease and length of total exposure (the total number of years of work in the shoe industry) or specific exposure (the number of years of work in the activity performed at the onset of the disease).

The mean total exposure was 5.4 years in Group I, 6.8 years in Group II, and 11.7 years in Group III; the mean specific exposure was of 3.4, 1.7, and 3 years respectively in the three groups. Some workers were affected by the disease after only one month of work. Fig. 1 shows the relationship between the time of year and the onset and severity of the disease. The most serious form of the disease (Groups I and II) begins with overwhelming prevalence in the winter and early spring; 83% of the cases in Group I and 74% of those in Group II were first manifested during the first four months of the year. The less serious form (Group III) manifests itself during all periods of the year with almost equal frequency. It is necessary to point out, however, that sometimes it was difficult for patients in this group to state with absolute certainty the month when the symptoms first began, as this was usually many months earlier.

The patients in Groups I and II were therefore

TABLE 2
DISTRIBUTION OF CASES OF POLYNEUROPATHY

Origin		Factories with cases of polyneuropathy (no.)	%	Cases of polyneuropathy (no.)	%
Region	Province				
Marche	Ascoli Piceno	46	63.9	71	58.2
	Macerata	15	20.8	22	18.1
	Pesaro	3	4.2	13	10.6
Umbria	Perugia	4	5.5	7	5.7
	Terni	1	1.4	1	0.8
Toscana	Arezzo	2	2.8	7	5.7
	Siena	1	1.4	1	0.8
Total		72	100	122	100

TABLE 3
RELATIONSHIP BETWEEN OCCUPATION AND SEVERITY OF POLYNEUROPATHY

Occupation	Cases (no.)	% of total	Severity of polyneuropathy		
			MMCV of PN		
			Group I (< 35 m/s)	Group II (35-44 m/s)	Group III (≥ 45 m/s)
Glueing	56	45.9	15	19	22
Cleaning	31	25.4	6	19	6
Other jobs (without direct contact with glues or solvents)	35	28.7	16	4	15
Total ..	122	100	37	42	43

TABLE 4
RELATIONSHIP BETWEEN SEVERITY OF POLYNEUROPATHY AND AGE, SEX, LENGTH OF EXPOSURE

Severity of polyneuropathy MMCV of PN	Age (years)		Sex		Length of exposure (years)			
	Mean	Range	M (no.)	F (no.)	Total		Specific	
					Mean	Range	Mean	Range
Group I < 35 m/s	31.4	15-54	8	29	5.4	0.1- 9	3	0.1- 9
Group II 35-44 m/s	35	15-52	9	33	6.8	0.1-22	4.1	0.1-10
Group III ≥ 45 m/s	38.1	19-59	22	21	11.7	0.7-31	7.3	0.3-23
Total ..	35	15-59	39	83	8	0.1-31	4.8	0.1-23

subdivided according to their jobs and to the month of onset of the disease, in order to evaluate whether or not the activity influenced the period in which the disease manifested itself (Fig. 2).

The polyneuropathy is prevalent during the early months of the year, regardless of the job performed, suggesting that the responsible agent might be the same in each job.

Observations concerning the work places

The most significant and constant elements that emerged from our visits to the factories where cases of polyneuropathy were found were:

- the disease was almost always found in very small factories with fewer than 20 workers;
- the work place was often a single, very small room, at ground level or in a basement. In the cold months the doors and windows were kept closed during work;
- all the leathers, glues, solvents, and the parts already glued or cleaned with solvents were kept in the work room. The glues and solvents were kept in open widemouthed containers on the

work table, very close to the people who used them;

all the work places lacked devices for eliminating gaseous pollutants and for ensuring an adequate air change;

because of the small dimensions of the work places, the workers were close to each other and, therefore, even workers who had no direct contact with glues or solvents were exposed to high concentrations of vapours;

none of the workers was aware of the possible hazards from exposure to the substances used, and personal hygiene was very poor.

Discussion

The most significant elements that emerge from our study are that: the frequency of the disease is steadily increasing and polyneuropathy in its more serious form manifests itself most frequently during the early months of the year. Even though the disease more frequently affects workers involved in glueing, it also affects those involved in cleaning

FIG. 1. Relationship between the severity of disease and month of onset of polyneuropathy.

the shoes with solvents and even those who have no direct contact with either paste adhesives or solvents. The disease is found almost exclusively among workers in small shoe factories, of the artisan type, where standards of hygiene are low.

These data cast doubt on the hypothesis that the agent responsible for the disease is contained only in the paste adhesives and is absorbed through the skin (Cappellini *et al.*, 1968). These observations limit, in our opinion, the importance of TOCP as the causative agent of the disease. In addition, analyses of many samples of glues and leathers taken in factories where cases of polyneuropathy occurred, showed that TOCP was either absent or present in negligible quantities (Crepet *et al.*, 1968; Cappellini *et al.*, 1968).

It seems more probable that the disease is caused by volatile substances that accumulate in the working environment under conditions of poor hygiene. The most likely hypothesis is that the primary causative agents are paraffin hydrocarbons of low boiling point (pentane, hexane, heptane, and isomers), without excluding at the moment the importance of other volatile and non-volatile substances present in the materials used.

This hypothesis is supported by the following evidence:

These hydrocarbons are able to cause a polyneuropathy as has been recently demonstrated in

FIG. 2. Relationship between activity and month of onset of polyneuropathy (Groups I and II).

experimental studies (Kurita, 1967; Truhaut *et al.*, 1973).

They have been found in very high concentrations (more than 80% of the total solvent) in glues and cleaning fluids collected by us from five different factories which had a total of 20 workers affected by the disease (Table 5). They were also present in similar concentrations in a glue considered responsible for 40 cases of polyneuropathy which occurred in Naples in 1973 (Collettivo medicingegneri contro la nocività, 1974).

An investigation conducted in shoe factories in the Marche region (Alberti, 1972, personal communication), where most of our patients came from, showed that in 75% of the work places examined the concentration of these substances was much higher than the threshold limit value proposed by the American Conference of Governmental Industrial Hygienists.

There are many similarities between our findings and those of Japanese authors who reported cases

TABLE 5
COMPOSITION OF SOLVENTS AND GLUES USED IN FIVE FACTORIES WITH A TOTAL OF 20 CASES OF
POLYNEUROPATHY

Solvent components		Boiling point (C°)	Solvent composition (% by weight)						
			Factories						
			1		2	3		4	5
			Glue (a)	Glue (b)	Cleaner	Glue (a)	Glue (b)	Cleaner	Glue
Paraffin hydrocarbons ..	Isopentane ..	31					11.5		
	Pentane ..	36			0.4		44.9	traces	0.2
	Pentane, 2-methyl ..	60	2.4				0.9		
	Pentane, 3-methyl ..	64	38.1	10.5	23.7	37.9	10.1	30	21
	n-hexane ..	69	46.3	71.6	62.2	49.7	15.1	49.3	60.6
	Iso-heptane ..	95					6.6		
	Heptane ..	98	8.4	13.1					
Total ..			95	95	86	88	89	79	82
Cyclic hydrocarbons	Cyclopentane ..	50			0.44		4.2	0.4	0.3
	Cyclopentane, methyl ..	72	2.2		13.2	12	2.7	17	17.4
	Cyclohexane ..	80		2.2		0.5	4	0.9	0.6
Total ..			2	2	14	12	11	18	18
Other	Toluene ..		2.5	2.6		traces	traces	2.4	
	MBK etc. ..								

of polyneuropathy attributed to n-hexane (Yamada, 1967; Miyagaki, 1967; Sobue *et al.*, 1968; Inoue *et al.*, 1970). These similarities include the type of work, the clinical picture, the epidemiological data, the poor hygienic conditions of the work places, and the composition of the solvents used.

Methyl n-butyl ketone (MBK) another industrial solvent, recently shown to cause peripheral polyneuropathy in man and in experimental animals (McDonough, 1974; *Journal of the American Medical Association*, 1974; Mendell *et al.*, 1974; *American Industrial Hygiene Association Journal*, 1975; Spencer *et al.*, 1975) has not been found in glues or solvents taken from shoe factories analysed by us.

The hypothesis that could explain the occasional occurrence of shoe-makers' polyneuropathy is that the disease is caused by factors acting together.

Important factors are the use of glues and/or solvents containing paraffin hydrocarbons with a low boiling point (pentane, 2-methyl-pentane, 3-methyl-pentane, hexane, heptane, etc.); poor environmental hygiene (small work places without any system for removing toxic vapours), and bad personal hygiene. These factors alone may be insufficient to provoke the disease which is precipitated when other factors are also present.

These additional conditions are the use of glues and/or solvents with an exceptionally high content of paraffin hydrocarbons with a low boiling point; increased environmental pollution such as occurs during the cold season as a result of closed doors and windows; the occasional presence of other neurotoxic substances in the materials, the role of which cannot for the present be excluded from the aetiology of the disease.

There are numerous indications that the paraffin hydrocarbons with low boiling points are the principal causes of the disease.

It is not at present clear, however, whether only one of these substances or the combined action of several hydrocarbons of the same group is responsible.

It is also not known why the disease sometimes occurs in a form so mild as to permit normal or almost normal work for months, while at other times it evolves rapidly and causes complete paralysis of the limbs within one to two months. It is possible that this effect is due to differences in the quantity of the toxic vapours absorbed by the workers, as a consequence of diversity in environmental pollution of work places.

Further experimental, clinical, and epidemiological studies are necessary to answer these aspects of the problem.

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