J. Neurol. 214, 137—152 (1977)

Journal of
Neurology

Toxic Polyneuropathies after Sniffing a Glue Thinner

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Summary. In West Berlin in the autumn of 1975 through the following 5 months we observed 18 juvenile patients who had a toxic polyneuropathy and had sniffed a glue thinner. The neurological picture consisted of a symmetrical, progressive, ascending, mainly motor, polyneuropathy with pronounced muscle atrophy and characteristic vegetative alterations. The height of the disease was reached after 1½—2½ months and was characterized by tetraplegia in 7 patients. After 8 months all patients still had a motor deficit. Nerve biopsy showed paranodal axon swelling, dense masses of neurofilaments and secondary myelin retraction. The neurological and morphological data correspond to the "glue sniffer's neuropathy" and the n-hexane and MBK polyneuropathy after industrial exposure, as described in 10 cases to date. However, there was no MBK in the glue thinner. The polyneuropathies occurred in close time relation with the denaturation of the thinner with MEK (2-butanone). It is concluded from the data n-hexane and MBK have a common toxic mechanism with primary axonal changes and that there is an additional synergistic effect of MEK.

Key words: 2-butanone – Glue thinner – Morphological data – Methyl-ethyl-ketone (MEK) – Nerve biopsy – n-hexane – Pattex – Sniffer's neuropathy – Polyneuropathy.

Zusammenfassung. Ab Herbst 1975 traten in West-Berlin innerhalb von fünf Monaten 18 Fälle toxischer Polyneuropathien bei Jugendlichen auf, die einen Klebstoffverdünner geschnüffelt hatten. Das neurologische Syndrom bestand in einer symmetrischen, progressiven, von distal aszendierenden, vorwiegend motorischen Polyneuropathie mit ausgeprägten Muskelatrophien und charakteristischen vegetativen Veränderungen. Der Höhepunkt der Erkrankung war nach 1½ bis 2½ Monaten erreicht und führte in 7 Fällen zu Tetraplegien; nach 8 Monaten waren noch bei allen Erkrankten motorische Ausfälle vorhanden. Nervenbiopsien zeigten paranodal Axonanschwellungen, Verklumpung der Neurofilamente und sekundäre Myelinretraktionen. Neuro-

logische und morphologische Daten entsprachen der bisher in 10 Fällen beschriebenen „glue sniffer's neuropathy" sowie den n-Hexan- und Methyl-Butyl-Keton(MBK)-Polyneuropathien nach industrieller Exposition. MBK war jedoch im Verdünner nicht enthalten. Die Polyneuropathien traten in direktem zeitlichen Zusammenhang mit der Vergällung des Verdünners mit Methyl-Ethyl-Keton (MEK) auf. Aus den Daten wird auf einen n-Hexan und MBK gemeinsamen Schädigungsmechanismus mit primär axonalem Angriffspunkt sowie einen zusätzlichen synergistischen Effekt des MEK geschlossen.

Introduction

„Sniffing" means the deliberate, abusive inhalation of volatile chemicals, such as solvents, aerosols or glues for their euphoric properties. This special kind of intoxicant abuse by adolescents has been observed for a long time in most industrial nations. Considering the extremely high concentrations of the substances inhaled, sniffing frequently signifies, in the individual case, an involuntary human inhalation experiment with fatal consequences [8, 26]. Sudden sniffing deaths by plastic bag suffocation or because of severe cardiac arrhythmia after aerosol inhalation have been described comprehensively [4, 11, 27]. In recent years, damage to the peripheral nervous system following chronic glue sniffing has occurred in Japan and in the USA and are referred to as "glue sniffer's neuropathy" [13, 14, 19, 23, 28, 31, 32].

Since about 1968, a glue solvent, the so-called Pattex thinner, has been sniffed by West Berlin adolescents and children [30]. Sniffing constitutes a process in which small portions of the liquid are poured into a plastic bag, less frequently into a piece of cloth, and the rising fumes are inhaled over a long period of time. In cases of chronic abuse, daily consumption amounts to about half a liter; inhalation periods can extend to 10 to 12 hours. Exposure periods of 5 to 7 years are not unusual among chronic sniffers. The intoxication consists of a euphoric, narcotising and only slightly hallucinogenous effect.

From 1968 till 1975, no chronic damages to health were observed among sniffing juveniles in West Berlin, although the abuse was, according to sales statistics, very extensive, and the number of sniffers was, at times, estimated at 2,000. In the autumn of 1975, there was an outbreak of polyneuropathies, which will be reported below.

Epidemiological and Chemical Data

The fact that no neurotoxic effects were observed from 1968 till August 1975, in spite of a high number of chronically sniffing juveniles, led us to the conjecture that a change had taken place in the composition. The producer denied this at first and stated as the constituents in October 1975 were: 41% benzine, 29% toluene, 30% ethyl acetate.

All the sniffers affected, however, reported that a new, badly tolerated thinner had been on the market since the early summer of 1975, which clearly differed

Table 1. Pattex thinner composition

Pattex-thinner — Aug. 22, 1974		Pattex-thinner — Oct. 22, 1975	
n-hexane	31%	n-hexane	16%
remaining benzine fraction	11%	remaining benzine fraction	26%
ethyl acetate	28%	ethyl acetate	18%
toluene	30%	toluene	29%
		methyl-ethyl-ketone	11%

Table 2. Clinical data on 18 sniffers afflicted with polyneuropathies

Case	Age	Degree of severity	Peak in weeks	Begin of remission in weeks	Sniffing time in years	Yearly consumption of old solvent in liters	Total consumption of new solvent in liters
1	20	III	11	15	3	90	2.5
2	19	III	13	17	5	200	3.7
3	18	I	5	7	3	175	?
4	20	II	9	11	3	90	3.0
5	17	II	9	11	2	60	7.5
6	18	III	8	16	3	45	1.2–2.5
7	16	II	10	19	½	30	?
8	19	II	8	9	3	30	?
9	16	III	9	18	¼	30	?
10	20	II	9	11	7	175	2.5
11	18	III	9	19	6	175	3.7
12	16	II	8	10	5	175	2.5
13	17	III	10	18	3	30	6
14	19	III	10	12	5	175	?
15	17	I	5	7	2	30	2.5
16	18	II	7	10	1½	80	3
17	21	I	10	12	7	175	20 (?)
18	35	I	4	5	1	90	2.5
18	16–21 (35)	I: 5 cases Ø 6 weeks II: 6 cases Ø 9 weeks III: 7 cases Ø10 weeks		Ø 8 weeks Ø11 weeks Ø15 weeks	¼–7 years	30–200 liters	1.2–20 liters

from the old composition in smell and effect. The sniffers had made efforts to use only the old thinner. The annual consumption of the old composition was, according to subjective data, between 30 to 200 liters per annum. In contrast to this, the total amount of the new mixture consumed was comparatively small, 1.2 to 20 liters in toto (see Table 2).

Ten adolescents, some of whom had sniffed over long periods of time but had given up their abuse by the spring of 1975, did not show disturbed functions in the clinical or in the electrophysiological examinations.

We examined 2 samples each from the year 1974 and 1975 by way of comparison. The first sample was procured in August 1974 in connection with a sudden sniffing death due to plastic bag suffocation. The second sample was

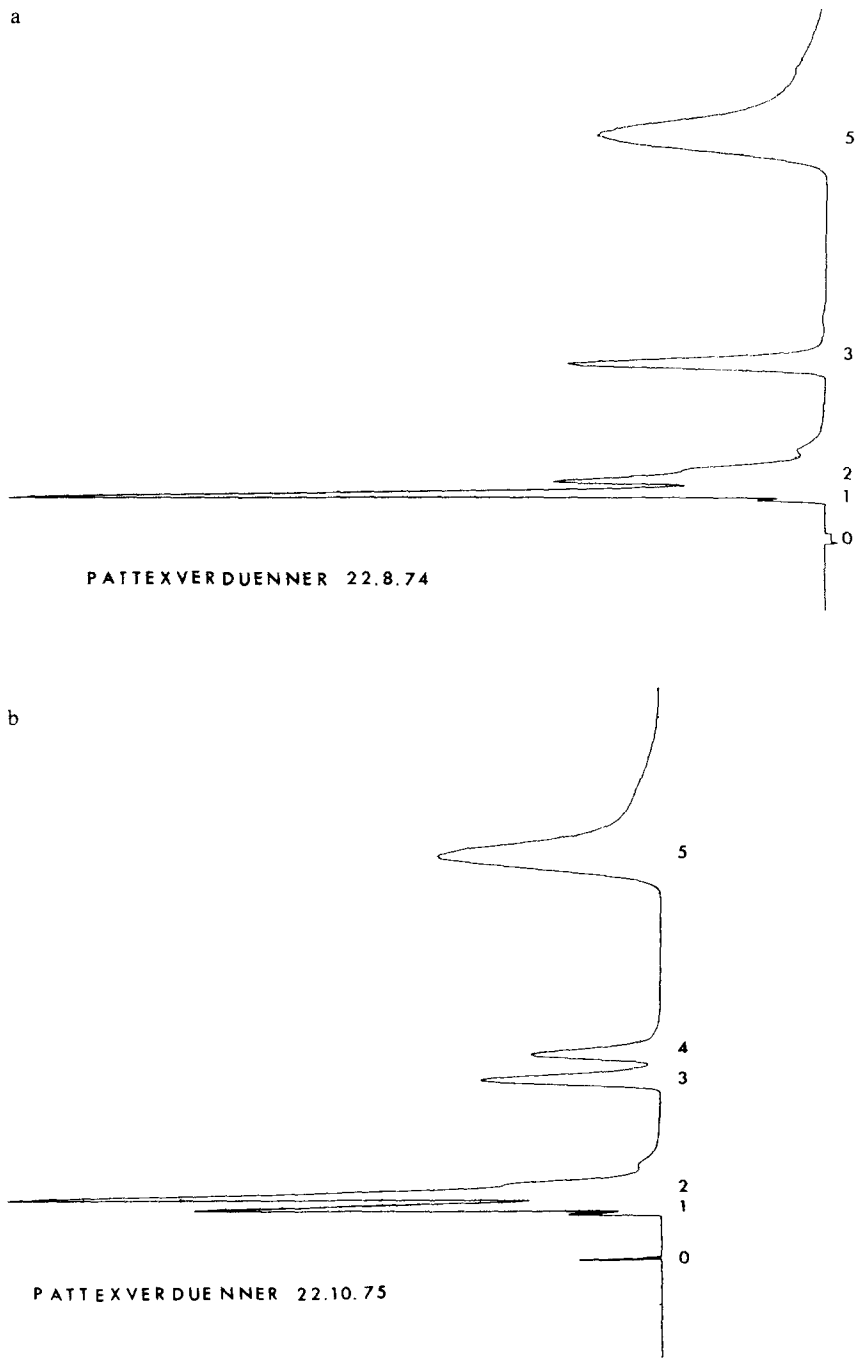

Fig. 1. Gas chromatograms of the Pattex thinner from Aug. 22, 1974 (a) and from Oct. 22, 1975 (b). *0* start; *1* n-hexane; *2* mixture of cyclohexane, cyclohexene, n-heptane, methylcyclohexane; *3* ethyl acetate; *4* 2-butanone (MEK); *5* toluene

bought on October 22, 1975 at a store at which 2 of the persons affected had regularly obtained the thinner.

Figure 1 shows the gas chromatograms[1] of the 2 thinner samples.

The results of the quantitative analysis are presented in Table 1.

The principal difference lay in the fact that methyl-ethyl-ketone (MEK; 2-butanone) appeared as a newly added substance in the October 1975 sample with a fraction of 11%. Furthermore, the composition of the benzine constituent had changed considerably. While in 1974, 33% of the total amount, i.e. 78.6% of the benzine constituent, fell to n-hexane, in 1975 the n-hexane amounted to only 16% (38.1%). The ethyl acetate concentration was reduced; the amount of toluene was not significantly changed.

In January 1976, the MEK containing thinner was taken off the market and replaced by the old MEK free composition. Although the abuse was continued in the spring of 1976, no further neuropathies occurred with one exception. This was a case of a 35 year old man who still continued to sniff the new solvent in February 1976, in spite of knowledge of its toxic effect.

Neurological Data

The clinical description of 4 cases has already been published by us elsewhere [2]. Table 2 gives a survey of 18 cases, the course of which we documented in the period of time from August 1975 till May 1976. We are dealing exclusively with male adolescents between 16 and 21 years of age and one 35 year old adult.

The neurological set of symptoms developed remarkably uniformly in all cases and varied only in the degree of severity and in the temporal course. In 10 cases, formication paraesthesias of the toes were the first symptom; in the rest, paraesthesias occurred simultaneously with weakness of the legs. The flaccid pareses ascended rapidly from the distal to the proximal in a symmetrical manner, which led within 2 to 3 weeks to paraparesis or paraplegia of the legs. Three weeks after the beginning of the illness, on the average, the pareses, also ascending from the distal to the proximal, spread to the arm muscles. In all cases, the extensors were first and most severely affected, and the ileopsoas and gluteal muscles were also involved. The head, neck and trunk muscles remained undisturbed.

In the early stage of the illness, severe muscle atrophies became evident (Fig. 2). While the deep tendon reflexes were no longer present in the first 3 weeks, the abdominal reflexes remained even in the later stages. Sphincter disturbances, pyramidal tract signs or cranial nerve disturbances were not detected.

A glove and stocking type sensory impairment was apparent on the hands and feet in the form of hypaesthesia, dysaesthesia, hyperpathia and pallhypaesthesia, which only rarely extended proximally over the area of the wrist or knuckle joints.

[1] *Method:* The gas chromatographic analysis was carried out with the apparatus HP 5750 Research Chromatograph with the packed column of carbowax 1500 (6 feet long, 4% coating). For the further analysis of the benzine component, a column with a 5% coating of silicone oil was used. In order to confirm the qualitative findings, the samples were examined by means of a GC/MS coupling (Varian Mat 111)

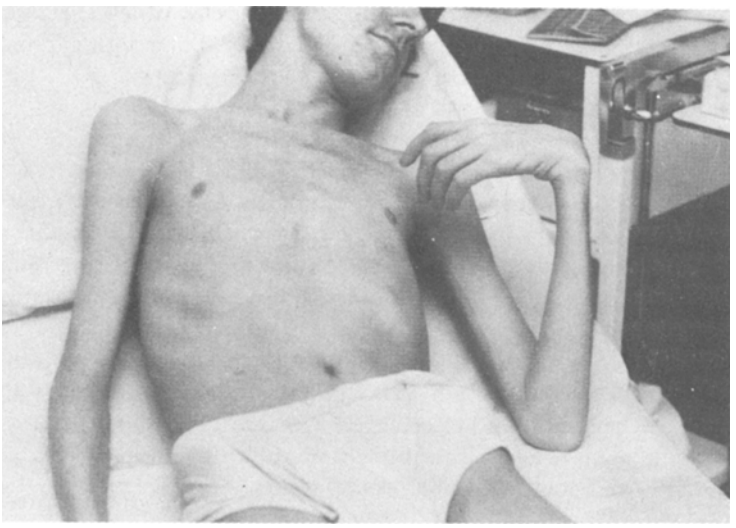

Fig. 2. Case 13: tetraplegia, muscle atrophies, especially of the upper extremities

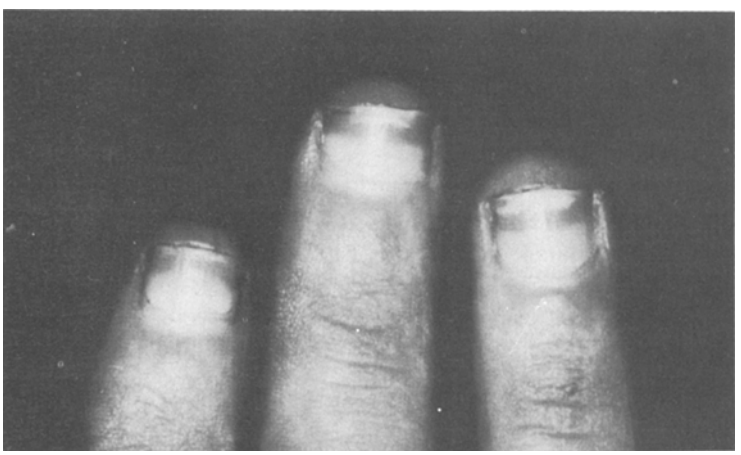

Fig. 3. Nail changes

In all cases the characteristic vegetative disturbances occurred. On the hands and feet there was an extremely pronounced hyperhidrosis, which led, in one case, to dyshidrotic eczema, and which, in 2 cases, later changed to anhidrosis. Hands and feet were discolored blue; the skin temperature was reduced in these regions. In 10 cases, changes in the nails occurred in the form of whitish stripes from 3 to 5 mm wide, which later grew out (Fig. 3).

The extent of the motor disturbances permitted the differentiation of 3 degrees of severity.

Group I. In 5 cases a milder form of the illness was apparent, which led to an extreme leg paresis, but which, at its peak, still permitted walking with support and which only discretely affected the arm muscles supplied by the radial nerve. The disturbance in walking, a waddling gait with the Trendelenburg phenomenon, genua recurvata and steppage gait, was a characteristic transitional stage in all cases.

Group II. The 6 persons affected could move only in a wheel chair at the peak of the paralysis. In the upper extremities, the hand muscles supplied by the radial nerve were nearly paralyzed; the upper arm muscles and the proximal arm muscles were extremely paretic.

Group III. 7 persons were tetraplegic at the peak of the illness.

Course

Although all patients discontinued their sniffing at the first signs of illness, the motor disturbances increased in all cases. The peak of the motor disturbances was attained, on the average, in the 6th week in Group I, in the 9th week in Group II and in the 10th week in Group III. The improvement began, on the average, two weeks later in Groups I and II and 5 weeks later in Group III, whereby the remission was first evident in the proximal muscles and then descendend.

The improvement proceeded very slowly in individual cases. In Group III there was still severe distal atrophy in all cases after 8 months.

While the proximal arm and leg muscles recovered relatively well, there was almost complete paralysis of the foot muscles and the hand muscles supplied by the radial nerve as well as extreme median nerve pareses and less severe ulnar nerve pareses. Flexion contractions of the ulnar fingers appeared. In Group II there was also atrophy of the lower legs paralysis, of the foot muscles and severe paresis of the hand muscles particularly of the extensors. In Group I, an extensor weakness could still be detected in the hands and feet after 7 months. Spastic symptoms were not observed in any of the cases. The deep tendon reflexes returned in the upper extremities in 6 cases towards the end of the period of observation. In almost all cases hyperpathia remained in the hands and feet as a residual sensory symptom, and the vegetative irritations had not yet receded at this point in time.

Additional Examinations

Internal Medical Findings

Serious carious changes in the teeth and a decrease in body weight were noticeable as secondary findings in the majority of the affected persons. Thorax X-rays furnished no further findings. Pulmonary function tests showed a lowered vital capacity and a reduced absolute seconds capacity in two tetraplegics. In both cases, impaired mobility of the diaphragm as an expression of phrenic nerve paresis was apparent on screening. In 2 patients of Group III, marked decalcification and, to some extent, patchy atrophy was noted in the X-rays of the hands and feet. Once there was a severe juvenile osteoporosis with a fish vertebra formation in the thoracic

part of the spine. ECG findings were normal. The EEG was normal except for slight diffuse disturbances in 4 cases.

Laboratory Findings

The routine diagnostic tests included: blood count, differential blood count, blood sedimentation rate, electrolyte, electrophoresis, SGOT, SGPT, Gamma-GT, LDH, CPK, alkaline phosphatase, blood sugar, creatinine, Quick test, lues serology, urinary status and sediment, determination of delta-amino-laevolic acid and porphyrine in urine as well as the Schilling test and determination of the antinuclear factors in some of the cases.

The following pathological findings were ascertained: in 4 cases an increased blood sedimentation rate (10/24, 10/25, 16/38, 30/50 mm according to Westergren); in one case slightly raised CPK levels (smaller than 100 IE/l) and in 3 cases slightly increased alkaline phosphatase levels (up to maximally 240 IE/l). In the latter cases, the patients already mentioned with radiologically visible bone changes are not being referred to.

Fluid Findings

Lumbar punctures were performed in 10 cases. The cell count was increased only in one case (25/3 cells). Once the total serum protein was in the upper area of the norm (449 mg/l), and once it was raised (752 mg/l) (norm value up to 450 mg/l). The rachialbuminelectrophoresis and the spinal fluid sugar were normal. A slight IgG increase, between 2.7 and 6.8 (norm value up to 2.2) was evident in 7 cases in which an immunodiffusion was carried out. The lues specific reactions in the fluid were always negative.

Neurophysiological Examinations

1. Nerve Conduction Velocity. An examination of the nerve conduction velocity (motor, sensory (antidromic)) was undertaken in all persons affected. Velocities were reduced in proportion to the degree of paresis. The same was true for the prolongation of the distal latencies. The conduction velocities of the lower extremities were, in part, no longer measurable due to the absence of response potentials.

Figure 4 shows the motor nerve conduction velocities in the median nerve in 17 patients at the time of admission.

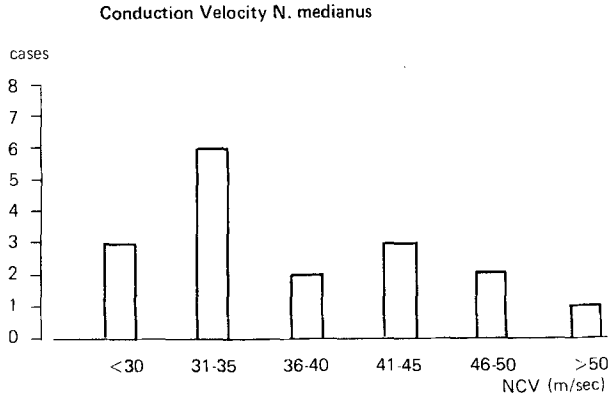

Fig. 4. Motor nerve conduction velocity of the median nerve in 17 affected persons at the time of admission

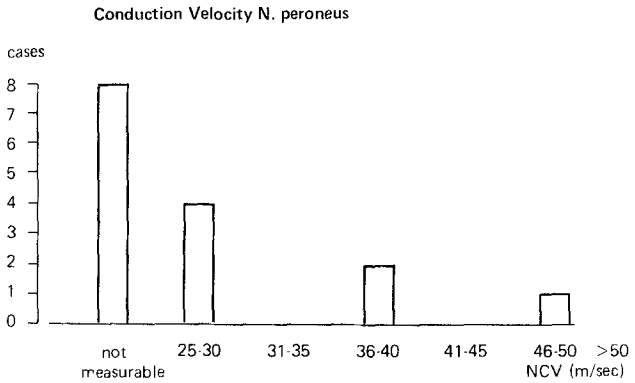

Fig. 5. Motor nerve conduction speed of the peroneal nerve in 15 affected persons at the time of admission

Fig. 6. Paranodal axon swelling. Absence of the filaments and tubuli. Myelin retraction (× 24,000)

Figure 5 shows the motor nerve conduction velocities of the peroneal nerve in 15 patients at the time of admission.

2. Electromyographic Findings. At the time of the first neurological examination, an electromyography was carried out in the majority of the patients, mainly on the following muscles of the lower extremities: anterior tibial muscle and femoral quadriceps muscle; of the upper extremities: dorsal interosseous muscle I, m. extensor digitorum communis and brachial biceps muscle. Findings which indicated damage to the peripheral motoneurone were universal. In addition to signs of denervation, such as fibrillation and positive sharp waves, there were signs of reinnervation in the form of small, protracted and polyphasic motor unit potentials. The extent of the reinnervation correlated with the duration of the disorder. In the first electromyographic examinations, 9 out of 13 cases showed positive sharp waves, 11 fibrillations and 8 reinnervation potentials in the described form. A myopathic pattern was never found.

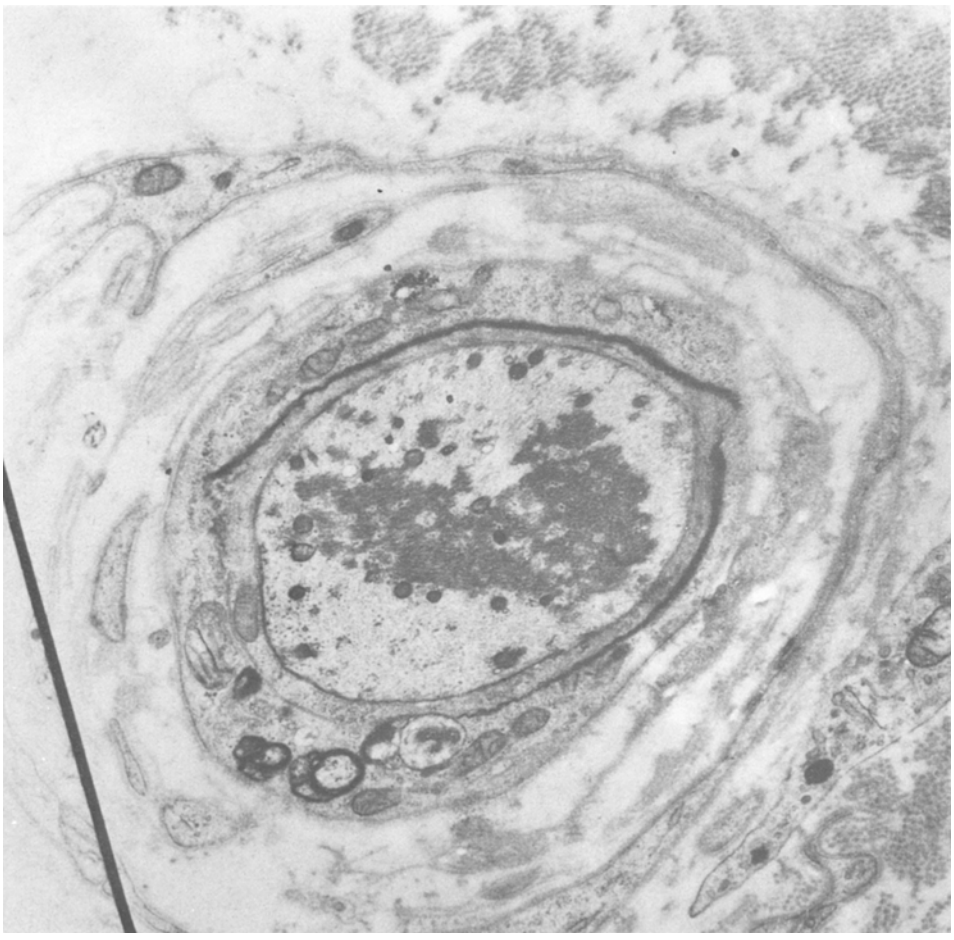

Fig. 7. Accumulation and clumping of the filaments. Myelin debris in the cytoplasm of Schwann's cell. Onion bulb formation (× 35,000)

Morphological Findings

Four biopsies of the sural nerve were taken and light and electron optically examined. For the ultrastructural examination, the nerves were fixed in glutaraldehyde and osmium tetroxide and embedded in micropal and araldite, sectioned with the LKB ultratome, contrasted afterwards with lead citrate and microscoped on a Zeiss EM 9. The semithin sections were stained with methylene blue. Muscle from the lower calf was also taken from all patients and examined as a frozen section histochemically (DPN, NADH, acidic phosphatase) as well as light-optically after staining with HE and Elastica-van Gieson. The muscles were also embedded in micropal for the electron optical examination and further treated like the nerves.

A lesion of the axon was the most conspicuous and most frequent finding on the electron optical picture of all nerve biopsies. This occurred in 2 types. One type involved exclusively paranodal axon swellings.

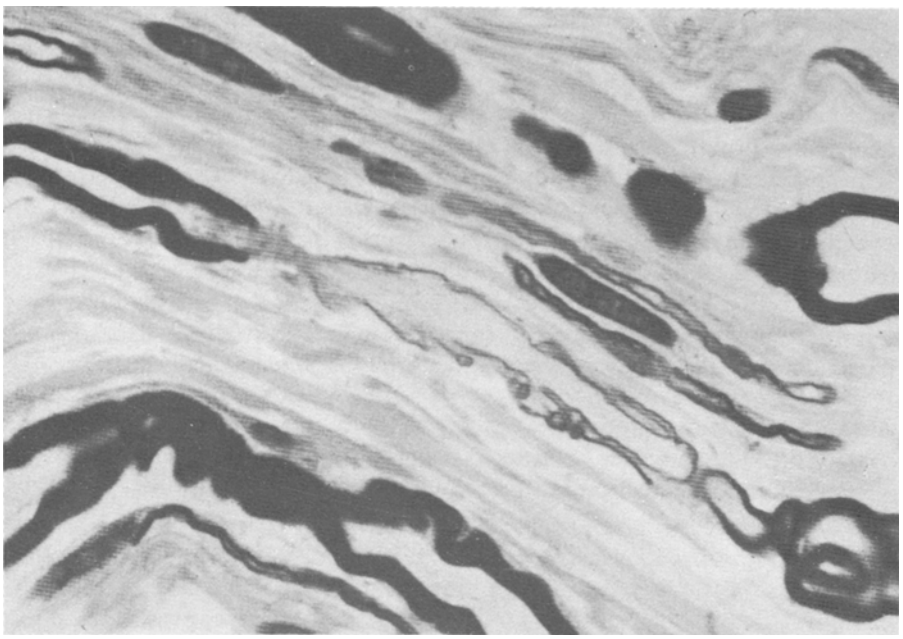

Fig. 8. Demyelination of an axon between two nodes of Ranvier (× 3,200)

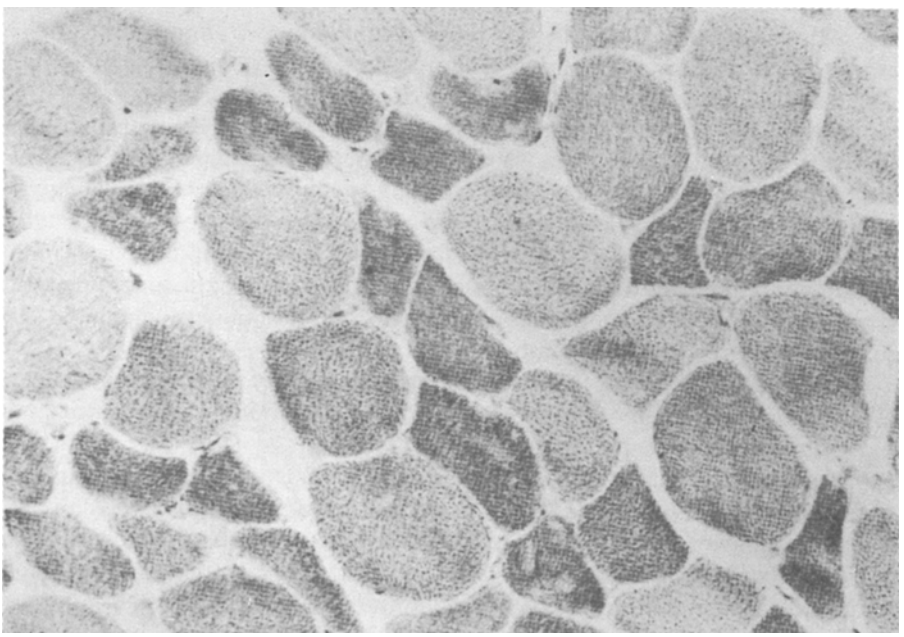

Fig. 9. Neurogenic atrophy. The type II fibres are reduced in diameter and deposited in groups; compensatory hypertrophy is apparent in the type I fibres

In such regions the axon was, apparently because of fluid deposit, almost empty optically but massively increased in volume (up to twice its diameter) and showed no organelles except for a couple of vesicles. In these zones the myelin sheath had retracted from the axon cylinder of Ranvier's node, which itself was widened. The myelin sheath became an extremely thin lamella (Fig. 6).

The second form of axon lesion was a densification of the cytoplasm together with a clumping of the neurofilaments. This change was always followed by demyelination. The myelin sheath of these densified axons was composed of a single cytoplasm duplication, while myelin catabolic products were evident in Schwann's cell (Fig. 7 and 8).

The primary damages of the myelin sheath were far less frequent than the axon lesions. Occasionally they were seen in the form of segmental demyelination (Fig. 8).

In advanced stages the muscles showed the clinical picture of neurogenic atrophy (Fig. 9). Moreover, violent disintegration of some muscle fibres, the appearance of target cells and the rounding of individual fibres could be observed.

Discussion

Recently a total of 10 individual cases of glue sniffer's neuropathy have been described in the Japanese and in the Anglo-American literature [13, 14, 19, 23, 28, 31, 32]. If one at first compares only the neurological set of symptoms in these cases with the Berlin cases, there is one principle point of conformity: sudden onset, rapid progression in spite of discontinuing use of the agent, symmetrical, from distal to proximal ascending distribution type of an almost exclusively motor polyneuropathy. These are the symptoms of glue sniffer's neuropathy as well as of the toxic polyneuropathy after sniffing Pattex thinner. The extensive muscle atrophy, the slight glove and stocking type of sensory disturbance, the unaffected function of the cranial nerves, and the characteristic vegetative symptoms are present in both syndromes. The lack of inflammatory fluid reactions and the almost exclusive manifestation of the toxin in the nervous system are common to both. Finally, the electrophysiological data and the clinical course are in agreement.

Either n-hexane alone [19, 32] or the combination of n-hexane and toluene [14, 23, 28, 31] have been regarded as the cause of glue sniffer's neuropathy up to the present.

In some cases, the paralyses occurred only in connection with hexane-containing glues [14, 19, 32]. Toxic neuropathies of the same type, but less pronounced, have been seen extensively after long industrial exposure to n-hexane concentrations between 500 to 2500 ppm under poor ventilation conditions [3, 6, 12, 16, 34, 35, 36, 37]. Furthermore, the neurotoxicity of n-hexane has been be confirmed by animal experiments [18, 20, 25, 38]. Schaumburg [38] recently ascertained clinical and morphological signs of a peripheral neuropathy in rats after subcutaneous injection as well as after inhalation of pure n-hexane.

The pathological changes consisted of giant axonal swellings and fibre degeneration in the peripheral as well as in the central nervous system.

Judging from the animal experiments, toluene does not influence n-hexane metabolism [31]. Cerebellar degeneration was observed after long-term inhalation [15]. Since the case report of Heuser [17], it has also been assumed that toluene alone can lead to toxic neuropathies [14, 23, 28, 32]. Heuser described, in a 46 year old printing worker, a fine tremor in the hands and feet, lid fluttering and a weakness of the extremity muscles. More precise neurological, clinical or electrophysiological data are lacking, so that the since accepted assumption of a peripherally neurotoxic mode of action of toluene is certainly not valid on the basis of these data, especially since there was also alcohol abuse.

In the Berlin outbreak of poisonings, the following data speak unequivocally against n-hexane as the exclusive cause:

1. In a number of sniffing adolescents, ultimately evaluated at 1000 to 2000, no organic damages were observed during the abuse of a thinner with a high n-hexane content over a period of 7 years.

2. The clinical picture of poisoning occurred when the n-hexane fraction had been decreased by more than half and methyl-ethyl-ketone had been added.

3. Juveniles who had discontinued sniffing by the spring of 1975 or who used only the old composition, were not affected; on the other hand, neuropathies occurred after 3—4 months in sniffers who had used only the new solution.

4. Even a relatively small amount of the MEK containing thinner led to neurotoxic damages, while comparatively very large amounts of the old composition were tolerated for a long period of time without consequences.

5. After the MEK containing thinner was taken off the market, new cases of the disease were not observed.

The characteristic morphological changes in the Berlin neuropathies were severe axonal lesions with paranodal axon swellings and secondary myelin retractions. Identical morphological findings were present in glue sniffer neuropathies, in industrial n-hexane polyneuropathies as well as in another solvent neuropathy, the methyl-butyl-ketone (MBK)-polyneuropathy [1, 5, 9, 10, 22]. 86 cases of this latter syndrome occurred in a fabric printing plant in Ohio in 1973 after methyl-isobutyl-ketone (MIBK) had been exchanged for MBK in a solvent mixture composed of methyl-ethyl-ketone (MEK) and MIBK [1, 5]. After the epidemiological data as well as by means of animal experiments, MBK was identified as a neurotoxin [24, 29]. A synergistic effect of MEK could not be excluded [1, 10]. Inhalation studies in rats showed a weakness of all limbs lasting a few hours after the exposure to MBK alone; after the inhalation of the combination MEK/MBK, however, the weakness remained for more than 24 hours [10]. In both groups, an axonal hypertrophy with perinodal and segmental breakdown of myelin was histologically evident. No neuropathies occurred after exposure to MEK alone.

It is interesting to note that n-hexane is oxydized to MBK by microorganisms [21]. Furthermore, according to the latest studies by Abdel-Rahman [39], n-hexane and MBK both have 2-hexanol and 2,5-hexanedione as common metabolites. Moreover, it seems significant that, in rats, MEK in combination with MBK increases the MBK serum concentration and enhances the neuro-

toxicity considerably [39]. The Berlin thinner did not contain MBK. The conclusion from analogy that MEK also increases the neurotoxicity of n-hexane significantly is suggested by our findings.

In view of a more precise inspection of the literature, combinations of n-hexane containing benzine mixtures with MEK were present in some cases of glue sniffer's neuropathy [14, 23] as well as in those of n-hexane neuropathies after industrial exposure [7]. Recently a toxic polyneuropathy was described by Viader [33] in a plastic worker who had worked two years under exposure to a 100% MEK solvent and a tetrahydrofuran-containing glue. The neurological set of symptoms was again comparable with the cases already described; morphological data are lacking.

A breakdown of the hexane-containing benzine mixtures by means of additional mass spectrometrical examinations was effected neither in the cases of glue sniffer's neuropathies nor in connection with the industrial n-hexane polyneuropathies. The exact composition is indefinite in many cases. Towfighi [32] describe 2 sniffer's neuropathies after abuse of a hexane-containing glue without giving data as to the amounts. Goto [14] leaves 42% and 39% of the constituents unexplained in two cases. Herskowitz [16] described 3 cases of industrial n-hexane polyneuropathies under the assumption that chemically pure n-hexane was being dealt with. Yamamura [37] specifies, in 93 cases of industrial n-hexane polyneuropathies, 70% or more n-hexane, a small fraction of toluene and other compounds, such as methylpentane and methylcyclopentane. It remains open to question whether n-hexane was the sole causative agent in these cases.

After the animal experimental demonstration of enhancement of MBK neurotoxicity by concomitant MEK exposure [39], our findings demonstrate for the first time an MEK induced human toxic neuropathy, which is clinically and morphologically identical with the wellknown n-hexane and MBK polyneuropathies. Apparently in this group of solvent neuropathies, it is a matter of a uniform damage mechanism with a primarily axonal site of action, for which a common metabolite of n-hexane and MBK is responsible. Animal experiments on the interactions of MEK and n-hexane are presently being carried out by us. In view of the extensive industrial distribution of new types of solvent mixtures, the composition of which is often insufficiently known, the clarification of these problems is of great significance.

References

1. Allen, N., Mendell, J. R., Billmaier, D. J., Fontaine, R. E., O'Neil, J.: Toxic polyneuropathy due to methyl-n-butyl-Ketone. Arch. Neurol. **32**, 209—218 (1975)
2. Altenkirch, H., Mager, J.: Polyneuropathien durch Schnüffeln von Pattex-Verdünner. DMW **101**, 195—198 (1976)
3. Assouly, M., Siou, G., Cavigneaux, A.: Polynévrites par n-hexane. Arch. Mal. Prof. **33**, 309—310 (1972)
4. Bass, M.: Sudden sniffing death. JAMA **212**, 2075—2079 (1970)
5. Billmaier, D., Yee, H. T., Allen, N., Craft, B., Williams, N., Epstein, S., Fontaine, R.: Peripheral neuropathy in a coated fabrics plant. J. Occup. Med. **16**, 665—671 (1974)
6. DiBosco, M., Fonzi, S.: La polineuropatia cosidetta da collanti o dei calzaturieri. Riv. Infort. Mal. Prof. **61**, 665—692 (1974)

7. Cargill, C.: Polynévrites dans l'industrie du cuir et de la chaussure toxicité du n-hexane. Thèse, Paris VII, 1972
8. Collom, W. D., Winek, C. L.: Detection of glue constituents in fatalities due to glue sniffing. Clin. Toxicol. **3**, 125—130 (1970)
9. McDonough, J. R.: Possible neuropathy from methyl-n-butyl-Ketone. N. Engl. J. Med. **290**, 695 (1974)
10. Duckett, S., Williams, N., Frances, S.: Peripheral neuropathy associated with inhalation of methyl-n-butyl-Ketone. Experientia **30**, 1283—1284 (1974)
11. Gamage, J. R., Zerkin, E. L.: Inhalation of volatile substances. Report series of National Clearinghouse for Drug Abuse. Information series **30**, No. 1, July 1974
12. Gaultier, M., Rancruel, G.: Polynévrites et hydrocarbures aliphatiques. Eur. J. Toxicol. **6**, 294—296 (1973)
13. Gonzalez, E., Downey, J.: Polyneuropathy in a glue sniffer. Arch. Phys. Med. **53**, 333—337 (1972)
14. Goto, I., Matsumura, M.: Toxic polyneuropathy due to glue sniffing. J.Neurol. Neurosurg. Psychiat. **37**, 848—853 (1974)
15. Grabski, D.: Toluene sniffing producing cerebellar degeneration. Am. J. Psychiat. **118**, 461—462 (1961)
16. Herskowitz, A., Ishii, N., Schaumburg, H.: n-Hexane neuropathy. N. Engl. J. Med. **285**, 82—85 (1971)
17. v. Heuser, M.: Toluolsucht. Med. Klinik **63**, 1888—1890 (1968)
18. Ishii, N., Herskowitz, A., Schaumburg, H. H.: n-Hexane polyneuropathy: A clinical and experimental study. J. Neuropath. Exp. Neurol. **31**, 198 (1972)
19. Korobkin, R., Asbury, A. K.: Glue sniffing neuropathy. Arch. Neurol. **32**, 158—162 (1975)
20. Kurita, H.: Experimental studies on the effects of n-Hexane to albino rats. Jap. J. Ind. Health **9**, 672—677 (1967)
21. Lukins, H. B., Foster, J. W.: Methyl Ketone metabolism in hydrocarbon-utilizing myco bacteria. J. Bacteriol. **85**, 1074—1087 (1963)
22. Mallov, J. S.: MBK neuropathy among spray painters. JAMA **234**, 1455 (1976)
23. Matsumura, M., Snoué, N., Ohnishi, A.: Toxic polyneuropathy due to glue sniffing. Clin. Neurol. **12**,290—296 (1972)
24. Mendell, J. R., Saida, K., Ganasia, M. F.: Toxic polyneuropathy produced experimentally by methyl-n-butyl-Ketone. Science **185**, 787—789 (1974)
25. Miyagaki, H.: An electrophysiological study on the toxicity of n-Hexane on the peripheral nerve. Jap. J. Ind. Health **9**, 660—671 (1967)
26. Musclow, C. E., Awen, C. F.: Glue sniffing: Report of a fatal case. CMA J. **104**, 315—318 (1971)
27. Reinhardt, C., F. et al.: Cardiac arrrhythmias and aerosol sniffing. Arch. Environ. Health, Vol. **22**, 265 (1971)
28. Shirabe, T., Tsuda, T., Terao, A.: Toxic polyneuropathy due to glue sniffing (Report of two cases with a light and electronmicroscopic study of the peripheral nerves and muscles). J. Neurol. Sci. **21**, 101—113 (1974)
29. Spencer, P. S., Schaumburg, H. H., Raleigh, R. L., Terhaar, C. J.: Nervous system degeneration produced by the industrial solvent methyl-n-butyl-Ketone. Arch. Neurol. **32**, 219—222 (1975)
30. Steinke, M.: Über das Schnüffeln, eine Sonderform jugendlichen Rauschmittelmißbrauchs. Das Öffentl. Gesundheitswes. **34**, 703—707 (1972)
31. Suzuki, T., Shimbo, S., Nishitani, H., Oga, T., Imamura, T., Ikeda, M.: Muscular atrophy due to glue sniffing. Int. Arch. Arbeitsmed. **33**, 115—123 (1974)
32. Towfighi, J., Gonatas, N. K., Pleasure, D., Cooper, H., McCree, L.: Glue sniffer's neuropathy. Neurology **26**,238—243 (1976)
33. Viader, F., Lechevalier, B., Morin, R.: Polynévrite toxique chez un travailleur du plastique. Rôle possible du méthyl-éthyl-cétone. La nouvelle presse méd. **4**, No. 24, 1813—1814 (1975)
34. Wada, Y., Okamoto, S., Tagaki, S.: Intoxication polyneuropathy following exposure to n-Hexane. Clin. Neurol. **5**, 591—598 (1965)

35. Yamada, S.: An occurrence of polyneuritis by n-Hexane in the polyethylene laminating plants. Jap. J. Ind. Health **6**, 192 (1964)
36. Yamada, S.: Intoxication polyneuritis in the workers exposed to n-Hexane. Jap. J. Ind. Health **9**, 651—659 (1967)
37. Yamamura, Y.: n-Hexane polyneuropathy. Folia Psychiatr. Neurol. Jap. **23**, 45—57 (1969)
38. Schaumburg, H. H., Spencer, P. S.: Degeneration in central and peripheral nervous systems produced by pure n-hexane: An experimental study. Brain **99**, 183—192 (1976)
39. Abdel-Rahman, M. S., Hetland, L. B., Couri, D.: Toxicity and metabolism of methyl n-butyl ketone. Am. Ind. Hyg. Assoc. J. **37**, 95—102 (1976)

Received July 16, 1976