TCE - CNS

Evidence for peripheral neurotoxic effect of trichloroethylene

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THE ANALGESIC and anesthetic properties of the chlorinated hydrocarbon, trichloroethylene (TCE), are well recognized.[1–3] Its value as a grease solvent and extracting agent has been appreciated by industry for many years.[4] The possible neurological manifestations of trichoroethylene poisoning were pointed out as early as 1915 by Plessner[5] and more recently by workers in the fields of industrial medicine[4,6–8] and anesthesiology.[9–11] Case reports describing cranial neuropathies following inhalant anesthesia using this material have been numerous.[12–16] The most common finding associated with trichloroethylene intoxication, trigeminal neuropathy, has been so well accepted that intentional exposure to TCE has been considered a useful treatment for tic douloureux.[17,18]

That trichloroethylene was selective in its action on the trigeminal nerve was questioned by Glaser[18] when he noted that this substance was capable of producing sleep. He suggested that TCE was not specific for the trigeminal tract or its sensory roots but rather depressed the cortex, affecting perception of painful stimuli. In agreement, Jackson[10] believed that TCE acted directly on the central nervous system, producing a general analgesia in which the trigeminal nerve connections were affected initially.

Experimental or quantitative measurements of peripheral nerve function under conditions of TCE intoxication have been reported. Hardy, Wolff, and Goodell[19] measured the pain threshold on the forehead and on the back of the head in 3 human subjects after inhalation of 1 ml. of TCE. In these areas, the pain threshold was increased nearly 45% after fifteen minutes but lasted for one hundred twenty minutes on the forehead as compared with forty minutes on the back of the head. This pointed to more efficient analgesia in the trigeminal territory and did not support the notion of a central nervous system mechanism for the analgesia. Rubinstein et al.[20] observed blood pressure responses following stimulation of the afferent sciatic nerve fibers or dura (trigeminal nerve supply) in the waking dog. These responses were eliminated in the presence of TCE anesthesia, suggesting that this substance produced its effects through an anesthetic action capable of depressing trigeminal and sciatic sensory pathways. Additional data from acute animal experimentation reported by Defalque[21] showed little difference between the effects of TCE upon reflexes mediated by the trigeminal nerve or a spinal nerve. He found that the pulp-chewing reflex (trigeminal) and the skin-twitch reflex (spinal nerve) were depressed equally in intensity and duration in the presence of trichloroethylene. In a critical review of the literature concerning TCE since its discovery by Fisher in 1864, Defalque[22] emphasized that the toxicology of trichloroethylene is still controversial because of a lack of careful clinical observations and

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experimental studies, especially regarding evidence for selective or specific analgesic effect on the fifth nerve.

This communication deals with the studies of the toxic effects of TCE on the peripheral and cranial nerve function in a young man following exposure to warm vapors produced by a degreasing machine utilizing trichloroethylene.

CASE SUMMARY

A 26-year-old man investigated a leak in an overheated degreasing machine which utilized trichloroethylene. He had direct exposure to vapors for about five minutes and indirect exposure through a potassium tetroxide cannister gas mask without a fresh air supply for one and one-half hours. Although he felt somewhat giddy after the exposure, no symptoms appeared for the first ten to twelve hours. At that time, nausea and vomiting, blurred vision, and numbness of the face, mouth, and oral pharynx were present. Articulation and chewing were difficult because of facial and jaw muscle weakness. Neurological examination sixty hours after the exposure revealed a young man who was lethargic, passive, and easily confused. He was oriented in time and circumstance but had difficulty following simple commands. Aromas of tobacco and vanilla were recognized. Peripheral visual fields appeared constricted upon confrontation; when tested by perimeter and tangent screen, a definite constriction of the visual field was found (Fig. 1). These constricted visual fields were checked by appropriate changes in the size of object as well as distance in relation to the screen, and repeatability of the findings ruled out an emotional basis for visual field defects of a constricted and a contracted type. Optic nerve heads were not elevated and good vascularization was present. The right pupil measured 6 ml. and the left pupil measured 4.5 ml.; both reacted to light directly and consensually. The left pupil did not react to accommodation as did the right one. Anesthesia to all modalities, including pinprick, touch, cold, and two-point discrimination was present in the entire distribution of the trigeminal nerve bilaterally. Corneal anesthesia was present bilaterally. Moderate limitation of lateral movement of both eyes was noted. Diplopia was present upon red lens testing. The left upper eyelid covered one-third of the upper half of the iris. There was flattening of the nasolabial folds bilaterally (Fig. 2). Perception of taste over the anterior two-thirds of the tongue was reduced. Hoarseness of voice was noted. Tests of coordination were unremarkable. Deep tendon reflexes were present and equal throughout. Except for anesthesia of the face, sensation over the trunk, neck, and extremities was intact. Babinski signs were absent.

Fig. 2. Bilateral facial paresis was indicated by flattening of nasolabial folds, inability to furrow brow, and weakness in showing teeth. Left eyelid ptosis and miosis were also noted.

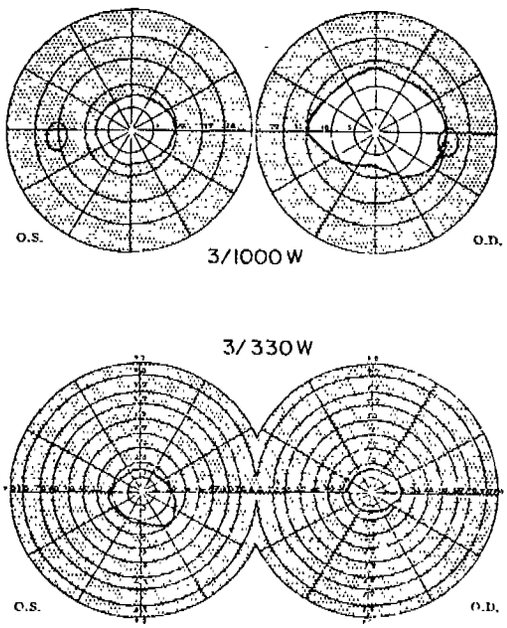

Fig. 1. The visual fields of the patient, determined three days after toxic exposure to trichloroethylene. Central (upper diagram) and peripheral visual fields (lower diagram) were constricted bilaterally.

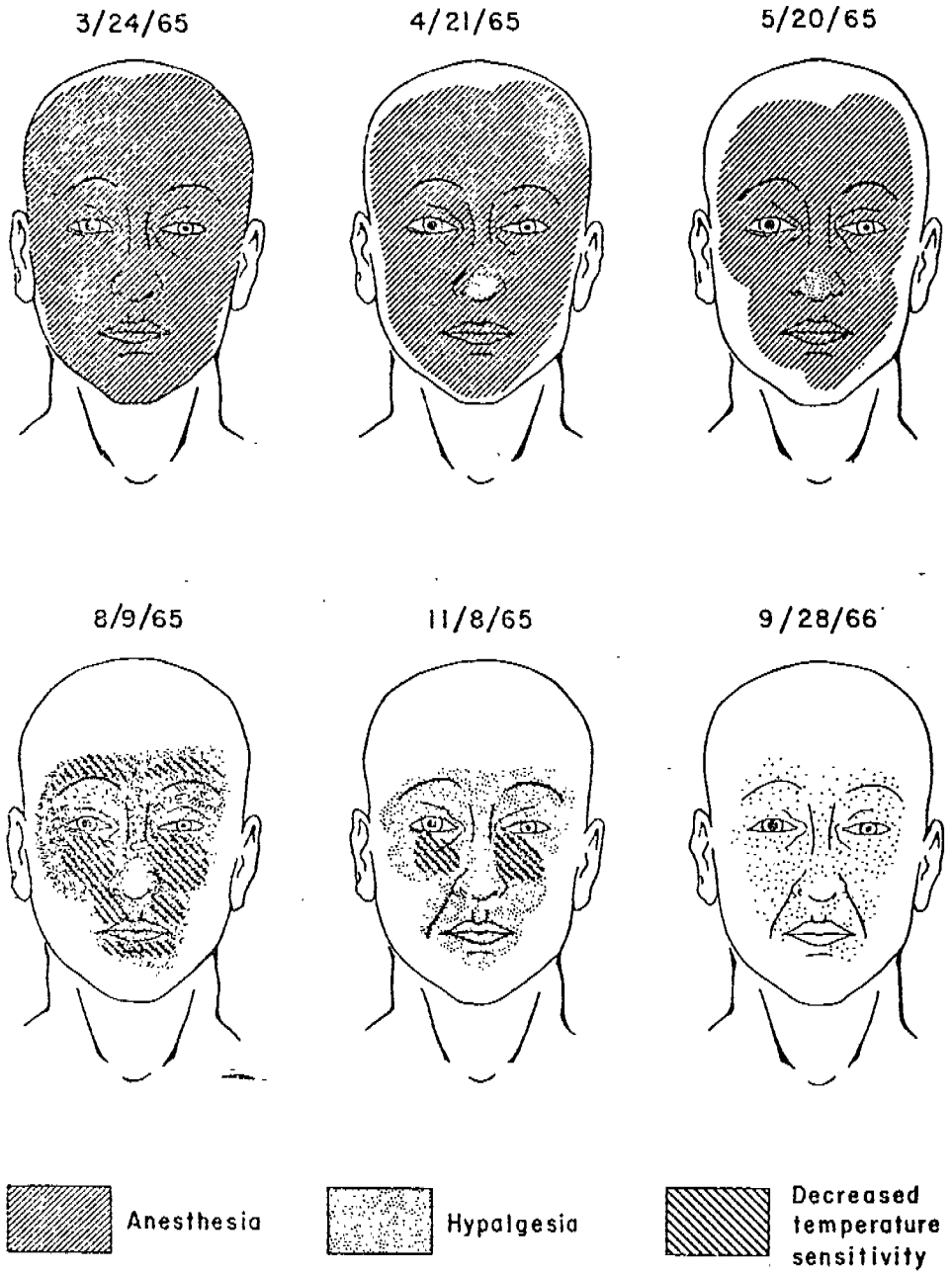

Fig. 3. Serial sensory maps showing complete anesthesia and subsequent recovery pattern. Note early return of sensation over tip of nose. Anisocoria and left ptosis of eyelid are depicted, as well as the return of the nasolabial folds.

Examination one month later revealed that the edge of facial anesthesia had receded from the periphery and the tip of the nose was hypalgesic rather than anesthetic, as were most other areas of the three divisions of the trigeminal nerve distribution. Subsequent examination revealed progressive recovery of sensation. It can be seen from Figure 3 that perception of pinprick initially returned in the periphery of the face and progressed in a concentric fashion toward the nasal-buccal region. The tip of the nose regained sensation to pinprick at about the same rate as did the edge of this anesthetic mask. The recovery on the face seemed asymmetrical in its exact distribution but

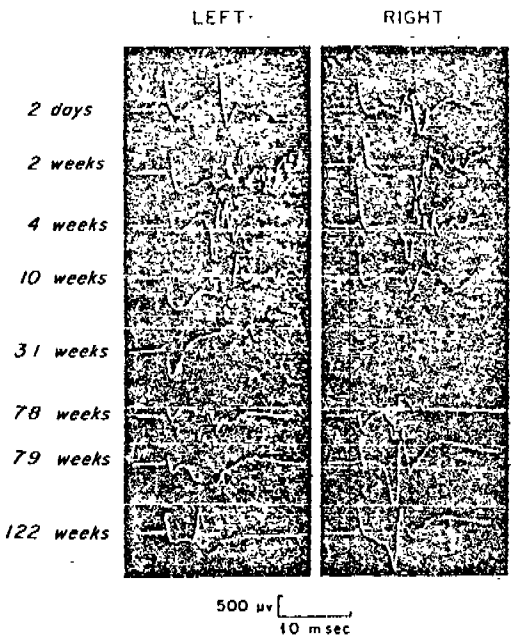

Fig. 4. Motor responses recorded with a bipolar needle electrode in the orbicularis oris following supramaximal percutaneous stimulation of the facial nerve. A progressive decrease in latency is seen over the period of one hundred twenty-two weeks (from top to bottom).

quite comparable in its rate in the three divisions of the trigeminal distribution. Motor function of the facial muscles, as well as strength in the masseter and pterygoid muscles, improved during this eighteen-month period. The vision recovered completely. Voice was normal and sensation had returned except for a slight dulling to pinprick in a patchy distribution.

Methods. Conduction velocities were determined in the fastest motor and sensory fibers in the ulnar nerve, using the equipment and techniques which we have previously reported.[23] The nerve was stimulated initially with threshold electric shocks in order to elicit the monosynaptic (H) reflex.[21,22] The stimulus intensity was then increased gradually to supramaximum to obtain the maximal direct motor response which was necessary to determine the motor conduction velocity. This stimulus obliterated the H reflex and evoked the antidromic motor (F wave) response.[21-26] The H reflex and the F response could be separated and were further evaluated by the following techniques: [1] rapid stimulation, 10 to 30 shocks per second, [2] tetanic stimulation (300 to 450 shocks per second) of the nerve for thirty seconds, followed by single test shocks of the same intensity for 2 to 1,000 msec., and [3] pairs of like stimuli to study the excitability cycles.[26,27] The velocities in afferent fibers in the ulnar nerve subserving the H reflex were determined between wrist and elbow and compared with the rate in the fastest motor and sensory fibers in the same segment. Recordings of at least 10 observations of each response were made with either surface electrodes (7-mm. silver disks) or intramuscular bipolar needle electrodes (0.3-mm. platinum wires with an interelectrode distance of 0.5 mm.).

The facial nerve was stimulated at the stylomastoid foramen and the motor responses were recorded in the orbicularis oris and oculi muscles.[28] The normal conduction time ranged from 2.2 to 3 msec. for the age group of 20 to 29 years[28,29] and was used as a basis of comparison in our patient. Serial recordings of responses were made initially at weekly and then monthly intervals.

Electrophysiologic results. The evoked motor responses in the orbicularis oris are shown in Figure 4. Polyphasic and complex motor unit potentials occurred after a prolonged latency early in the illness. A more synchronous response of muscle fibers appeared with recovery over the eighteen-month period. A similar prolongation of conduction time was observed in the facial nerve to the orbicularis oculi. The conduction times (latencies) in the facial nerve are plotted on the graph in Figure 5. Conduction velocity in the ulnar nerve was reduced only in distal sensory fibers at two weeks, as shown in the table. The velocities returned toward normal nine weeks after exposure but remained abnormal at thirty-four weeks, although the patient had no signs or symptoms referable to the ulnar nerve. The slowing of velocity in the ulnar nerve was sensory more than motor and distal more than proximal.

H reflexes, which usually cannot be recorded in normal adult hand muscles,[21,26] were present in the hypothenar muscles throughout the period of the testing (Fig. 6). The velocity in the afferent fibers was less than that in the fastest sensory and

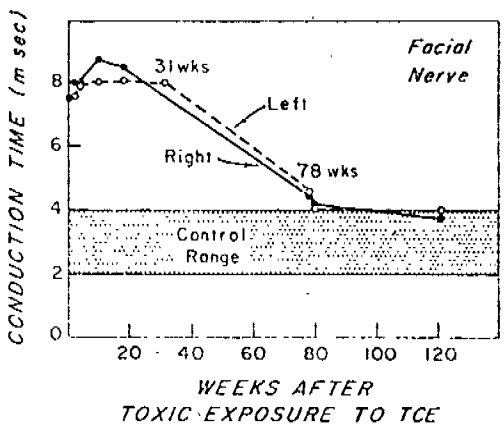

Fig. 5. The responses shown in Figure 5 are plotted on this graph to demonstrate the recovery curve of facial neuropathy following toxic exposure to trichloroethylene.

CONDUCTION VELOCITY IN ULNAR NERVE
(meters per second)

Time	Nerve action potentials: Finger-wrist	Wrist-elbow	Elbow-axilla
2 weeks	46	63	66
9 weeks	57	60	61
34 weeks	54	58	66
Normal	64.7 ± 3.9	64.8 ± 3.8	69.1 ± 4.3

Time	Motor: Wrist-muscle	Elbow-wrist	Axilla-elbow
2 weeks	2.8 msec.	53	60
9 weeks	2.5 msec.	51	61
34 weeks	2.8 msec.	50	58
Normal	2.7 ± .3	58.9 ± 2.2	64.4 ± 2.6

Time	H reflex: Wrist-elbow
2 weeks	48
9 weeks	47
34 weeks	48

motor fibers in the same segment. Posttetanic potentiation of the H response was observed but not of the F wave. The latency of the F response (24 msec., elbow to muscle) was the same as that of the H reflex. No abnormality of the F wave was observed.

DISCUSSION

Enderby[15] emphasized the rarity of cranial neuropathies associated with pure trichloroethylene anesthesia, finding only one case in 2,000 anesthetized patients. In that patient, soda lime contaminated the vapors. There appears to be no report of injury to cranial nerves by undoubtedly pure trichloroethylene.[29] Industrial trichloroethylene is said to impose injury in a frequency rate of 0.3 per million exposure hours.[8] The patient described in this report was the victim of acute poisoning by the trichloroethylene vapors and its probable breakdown products elaborated from a defective degreasing machine. Some authors believe that trichloroethanol is important in the pathogenesis of trichloroethylene poisoning,[30] while others[31] believe that there is no danger of trichloroethylene intoxication under clinical anesthesia unless the substance is brought into contact with an alkaline, when it may break down into hydrochloric acid and dichloracetylene. Industrial trichloroethylene contains alkaline substances or cresol. It volatizes and decomposes, under the influence of light, into phosgene, hydrochloric acid, and carbon monoxide, as well as dichloracetylene.[30,31] Dichloracetylene may, itself, decompose into phosgene and carbon monoxide. In the presence of moisture, dichloracetylene may hydrolyze to dichloracetyl chloride and further hydrolysis may produce the corresponding acid. The conditions in the poorly ventilated room in which our patient was working encouraged volatization of the material since the temperature was well over 100° F. Short exposure to the decomposition products of trichloroethylene may be sufficient to produce cranial neuropathies.[32–34]

In our patient, as in the workers first described by Plessner in 1915,[5] survival after exposure to TCE was accompanied by extensive anesthesia of the face, oral cavity, and tongue mucosa. Difficulty in chewing was present, partly because of anesthesia inside the mouth

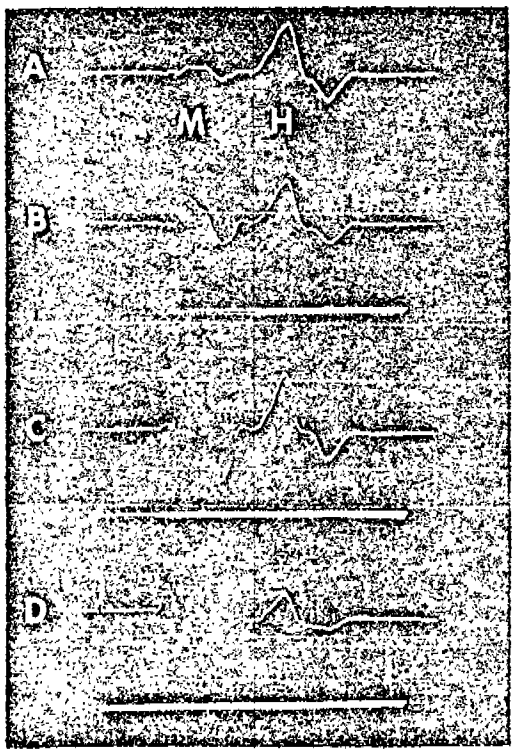

Fig. 6. Recordings of the H reflex (H) in the hypothenar muscle with [A] threshold stimulation. With increasing stimulus intensity [A through D], the (M) response was elicited and the H response was depressed. Calibration: 10 msec.

and partly because of weakness in the masticatory muscles. In most cases previously reported,[4,35–37] the trigeminal involvement was present for at least one year after cessation of the toxic exposure. According to Stuber,[1] the cranial neuropathy was not clearly a result of central damage of the roots, as in tabetic trigeminal neuropathy, nor clearly a peripheral neuritis because of the irreversible damage, the predilection for sensory fibers over motor fibers. Buxton and Hayward[16] reported 4 cases of cranial neuropathy following toxic exposure to industrial trichloroethylene. One of these patients, age 39, died after aspiration pneumonia before any return of facial sensation had occurred. The most striking finding on autopsy included bilateral extensive myelin and axon degeneration of the trigeminal nerve and its proximal root. In luxol blue and silver preparation, scarcely any myelinated axons remained; myelin was aggregated into irregular globules and axons were reduced in number.

Some of the reports in the literature carefully document the pattern of progression and recovery of sensory loss over the face. One patient (Case 4), described by Humphrey and McClelland,[18] showed total anesthesia for ten days before the skin over the forehead and cheeks felt "swollen and stretched." She also had a tingling sensation around the nose. Hypalgesia was present over the face except for an exaggerated response to pinprick on the nose. A second patient (Case 11), reported by the same authors, experienced subjective numbness in all divisions of the trigeminal nerve with paresthesia and initial recovery occurring over the nose. These two patients developed facial sensory loss after exposure to trichloroethylene anesthesia delivered by a machine containing soda lime and employing a "to-and-fro" method. One of the workers described by Buxton and Hayward[16] spent four hours in the warm vapors of trichloroethylene inside a tank and had initial circumoral numbness which developed into complete analgesia in the trigeminal distribution. In these cases, as well as the one presented in this communication, the onset of numbness occurred around the snout and spread centrifugally in the distribution of the fifth nerve. During recovery, our patient showed return of sensation in a centripetal, concentric, "onion-peel" pattern.

Sherrington[38] postulated that the skin field of the trigeminal nerve represented supply by peripheral nerve trunks rather than those of sensory nerve roots. Each division—ophthalmic, maxillary, and mandibular—was found to have a delineated area of supply reaching the midline with varying degrees of overlapping. Later authors, including Dejerine,[39] Kraus,[19] and Bing,[41] clearly defined the segmental sensory pattern of the face as well as peripheral nerve fields. Facial dermatomes have been depicted as having a concentric or "onion-peel" arrangement centering on the nose. The explanation of this sensation distribution is usually based on Dejerine's observation of progression of sensory loss associated with expanding cervicomedullary lesions such as syringobulbia, that is, facial segmentation is a reflection of the lamination of the nucleus of the spinal tract of the trigeminal nerve. The upper part of the nucleus innervates the field nearest the nose and the mouth, the intermediate part contains afferents from the semicircular area from the forehead to the chin, anterior to the ear, and the lower part receives input from the caudal area of the face.

There have been many attempts to correlate the receptive field location of trigeminal cutaneous afferents with the level of termination within the spinal tract. Van Valkenburg[42] reported that maxillary and mandibular divisions extend most caudally. The reverse observation has been made by others.[43–45] Dejerine's opinion that the termination of fibers within the spinal tract is related, not to the peripheral division in which they lie but to the distance of their receptive field from the perioral region, received support from recent histological studies in rat[46] and the cat and monkey.[47] Single unit recordings[48] have shown that tactile sensory fields terminate at all levels, extending caudalward to C_2. Other observations[49,50] revealed that small myelinated fibers within the tract do not extend beyond the obex in the cat. Wall and Taub[49] demonstrated that the largest peripheral trigeminal nerve fibers succeed in penetrating long distances from the root entrance zone, allowing for all sizes of peripheral nerve fibers to converge on the most rostral cells of the trigeminal nucleus, while the more caudal cells receive only the largest myelinated fibers. The rostral cells would correspond to the snout region while the most cau-

dal cells would correspond to the peripheral areas. A concentric sensory pattern is thus formed, based on a rostral-caudal nuclear arrangement of different fiber sizes.

Fewer C-fibers are found in the sensory branches of the trigeminal nerve than in comparable spinal nerves. Gerard[31] found only about 15% of unmyelinated fibers in the trigeminal sensory root. Wall and Taub[19] found no fibers smaller than 3μ. The smaller fibers are concentrated at the front of the face, around the tip of the nose and the snout, while the larger ones are in the back of the face, in the periphery of a concentric distribution. In this way, a condition which affects peripheral conduction, possibly by altering myelin, could produce a clinical picture of a concentric pattern of sensation loss. The clinical manifestations would first appear where the density of smaller fibers was highest and progress centrifugally. The recovery would occur in reverse pattern. The smaller fibers concentrated in the snout region may be affected more and sooner than the larger ones, the recovery may take place in the larger fibers moving from the back of the head forward. The "onion-peel" appearance of sensation loss could, therefore, be due to peripheral neuropathy by a decrease in the number of afferent impulses reaching the primary nuclei of the trigeminal system, rather than damage to the nuclei themselves.

In agreement with the suggestion of Simpson,[32] reversible slow nerve conduction velocity in our patient most likely is secondary to demyelination and remyelination. Stuber[4] postulated the action of TCE on nervous tissues to be a manifestation of its physical property as a lipid solvent and that this substance adsorbed to nerve membranes, resulting in anesthesia. When a toxic amount was present, there was an irreversible effect by extraction of lipid content rather than by adsorption. Although unproved, this explanation seems quite plausible in the predilection for peripheral nerves, sensory more than motor, and the manifestations in altered conduction characteristics, as demonstrated in this report. The conduction studies of the motor fibers of the seventh nerve, as well as the sensory and motor potentials studied in the ulnar and tibial nerves, provided inferential evidence that conduction characteristics of the fifth nerve may be similarly involved. MacDonald[33] found reduction in thickness or absence of myelin over variable lengths of nerve fibers in experimental diphtheritic neuropathy and considered this an important factor in reducing individual fiber conduction velocity. The application of saponin (a fat solvent, as is TCE) resulted in damage to the myelin sheaths and a delay of excitation at nodes of Ranvier.[34] If we assume that demyelinization resulting from the lipid solvent effect of TCE would alter the large and small fibers in proportion to the amount of myelin present, then there would be a possibility that the smaller fibers might be damaged proportionately and perhaps slowed even more than the larger ones. In the stage of complete anesthesia, all fibers would be affected, but as recovery ensued, the differences in sensation loss pattern of the face might coincide with the fiber spectra of different parts of the head. Gradual recovery in function would coincide with an increase in the number of fibers possessing reestablished conduction.[35,36]

SUMMARY

A young man with industrial trichloroethylene intoxication has been carefully studied. The interesting observations in this study include electrophysiologic evidence of a peripheral neuropathy and the clinical definition of the pattern of trigeminal sensory loss and recovery. The onion-peel distribution, usually indicative of segmental or nuclear trigeminal lesions, is best explained in this case by disturbed nerve conduction, possibly due to the lipid solvent effect of trichloroethylene on peripheral myelin sheaths.

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