

Nervous System Degeneration Produced by Acrylamide Monomer

by Peter S. Spencer* and Herbert H. Schaumburg*

Acrylamide, widely employed as a vinyl monomer in the polymer industry, is a potent neurotoxin to man and to animals. The cumulative effect of prolonged, low-level exposure to acrylamide monomer is the insidious development of a progressive peripheral neuropathy. Sensory symptoms begin in the hands and feet (numbness, pins and needles), certain reflexes are lost and, with severe exposure, muscle weakness and atrophy occur in the extremities. The peripheral neuropathy may be supplemented by symptoms indicative of central nervous system damage (ataxia, tremor, somnolence and mental changes).

The neuropathologic basis for this clinical picture has been determined in cats. Here, chronic acrylamide intoxication produces selective peripheral and central nerve fiber degeneration. Degeneration first occurs in the extremities of long and large nerve fibers which later undergo a progressive, seriate proximal axonal degeneration known as dying-back. Especially vulnerable are sensory axons supplying Pacinian corpuscles and muscle spindles in the hindfoot toepads, while adjacent motor nerve axons die back later. Distal central nerve fiber degeneration is seen in the medulla and the cerebellum.

The neurotoxic property of acrylamide is of practical concern in two areas. One major problem is the protection of factory workers engaged in the manufacture of acrylamide. A sensitive test of neurologic function in these individuals, i.e., touch sensation, based on the experimental observation of the exquisite vulnerability of Pacinian corpuscles in acrylamide intoxicated cats, is presently under consideration. The second area for concern is the exposure of the populace to minute amounts of neurotoxic acrylamide monomer which contaminate acrylamide polymers currently deployed in the environment. Federal restrictions on the maximum permitted exposure to acrylamide, based on a largely clinical study of acrylamide neurotoxicity conducted ten years ago, may require a re-evaluation in the light of recent advances which have pinpointed the initial sites of nerve fiber degeneration.

Monomeric acrylamide ($\text{CH}_2\text{CHCOCH}_2$) is a potent neurotoxin capable of producing nervous system degeneration in a wide variety of animals (1-8). This property was first recognized in the early 1950's during routine toxicological studies prompted by the advent of large-scale production of acrylamide monomer for the polymer industry. That acrylamide is neurotoxic to man was discovered in 1954, shortly after the commencement of manufacture of acrylamide from acrylonitrile, when several

factory workers developed peripheral nerve disease. Since this time, more instances of human acrylamide intoxication with peripheral neuropathy have been reported, in individuals engaged both in the manufacture and in the use of acrylamide monomer (9-13).

The present concern with the neurotoxic property of acrylamide monomer is related to the vast and increasing production of the chemical for the manufacture of high molecular polymers which enjoy important applications in industry and commerce (14). There are two areas for concern, both of which arise from the central features of acrylamide neurotoxicity that the effects of acrylamide are related to

* Department of Pathology (Neuropathology) and the Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, The Bronx, New York, 10461.

the accumulated dose and that the nervous system damage develops insidiously (2,4,15-18): one is the degree to which people employed to manufacture acrylamide are daily exposed to the neurotoxin, and second, the extent of the exposure of the populace through the deployment in the environment of acrylamide polymers contaminated with small amounts of acrylamide monomer (19).

Human Intoxication

Acrylamide intoxication in industry appears to result from repetitive daily local dermal contact (12,20). The small molecular size and great solubility promote the ready skin absorption of acrylamide (2). Commonly, contact with acrylamide is marked by a local dermatitis (21). Acrylamide intoxication may first become evident in the form of excessive fatigue, somnolence and weight loss (12). Signs of nervous system damage appear slowly; first in the feet and hands and later in the legs and arms. Individuals may complain of pins and needles, numbness, coldness, or excessive sweating (9, 22). Fine movements of the hands, such as writing and shaving, become noticeably difficult, and there may be an impairment of temperature sensation. Weakness in the hands and legs may progress to a frank loss of power with prominent atrophy of the small muscles of the hand. These neurologic signs may be correctly attributed to progressive peripheral nerve damage which begins in the distal extremities and proceeds proximally with time and maintained exposure. If individuals are removed from contact with acrylamide, the peripheral neuropathy slowly disappears although animal studies indicate a re-exposure may precipitate symptoms more readily (3,23). In addition to signs of peripheral neuropathy, some affected individuals developed signs of central nervous system damage such as tremor, an ataxic gait, or a mild organic mental syndrome (9,12,13).

Neuropathology

Peripheral nerve biopsies obtained from three patients recovering from acrylamide neuropathy were examined by Fullerton (24). In one, there was a marked loss of large diam-

eter nerve fibers, a pattern which was repeated in the nerves of baboons recovering from acrylamide neuropathy (25). Systematic study of the pattern of nerve fiber damage in experimental animals demonstrated that distal regions of nerves were more severely affected than proximal parts (4). It was possible to demonstrate in an individual nerve fiber that distal degeneration coexisted with proximal preservation (26). After animals had recovered for several months, the distal parts of affected fibers had undergone regeneration. These studies led to the conclusion that in acrylamide neuropathy nerve fibers undergo a slow, progressive retrograde degeneration, a pattern of damage termed "dying-back" (27,28).

Studies of other toxic industrial chemicals, for example the cresyl phosphates and methyl *n*-butyl ketone, have shown that, like acrylamide, these also produce dying-back axonal degeneration (29,30). It has been realized that the extremities of long and large nerve fibers are especially vulnerable and that these are the first to undergo the retrograde changes (25,28). It has also been demonstrated that in dying-back diseases the peripheral nervous system is not exclusively affected and that distal degeneration also occurs in certain long nerve fibers tracts of the central nervous system (31). Thus, in acrylamide-intoxicated cats, axonal degeneration occurs in the medulla, in the anterior and lateral columns of the spinal cord, and in the nerve terminals of the cerebellum (27,32,33). The recognition of a central nervous system component in acrylamide neuropathy was crucial since, unlike the peripheral nerve degeneration which can recover with time, central nervous system regeneration is unlikely to occur.

With the dying-back process in acrylamide neuropathy firmly established by previous investigators, we turned our attention to establishing the peripheral site at which axonal degeneration first occurred (28). Cats were slowly intoxicated with injected acrylamide and biopsies were repeatedly performed before and during the illness. Fine nerves, slips of muscle, and Pacinian corpuscles were sampled in hindfeet paws. In this way, we were able to examine the distal tips of some of the longest nerve fibers in the body; sensory nerves supplying Pacinian corpuscles, which detect touch and vibratory stimuli, muscle spindle primary

afferents which respond to muscle stretch, and adjacent motor nerve terminals which transmit impulses for muscular contraction. These studies revealed that Pacinian corpuscle axons began to degenerate first, sometimes before the onset of clinical signs; shortly thereafter, muscle spindle axon degeneration began and much later, adjacent motor nerve terminals started to change. This study demonstrated that certain sensory nerve terminals were more vulnerable to acrylamide than adjacent motor nerve terminals, a finding which seems to correlate both with clinical evidence of early sensory deficit and the proportionately greater and earlier impairment of electrical conduction in sensory nerve fibers (2,4,5,9,24,25).

Site of Neurotoxic Action

The basis for the neurotoxic property of acrylamide is unknown. Presumably, the property is related to the high reactivity of the acrylamide molecule which is not significantly metabolized *in vivo* (34,35). It has been proposed that acrylamide acts as a nicotinamide antagonist (17) and it has been demonstrated that the molecule is able to react with nervous system proteins (36).

The mechanism by which acrylamide produces dying-back axonal damage is also unknown. One explanation is that acrylamide interferes with the metabolic machinery of the nerve cell body which gradually fails in its function to provide material for the axon (37). This leads to a depletion in the amount of material reaching the distal regions of axons where degeneration begins (36,38). Another hypothesis suggests that acrylamide inactivates the axonal transport system by which substances, assembled in the neuron cell body, are transported along the axon (39,40). Finally, it has been suggested that if acrylamide inactivated a substance in the axon, which is dependent for its supply on the nerve cell body, this alone could account for the dying-back process (7,27,28). These theories have been discussed in detail elsewhere (33).

Protection of the Factory Worker

Education and hygiene are required to protect factory workers engaged in the manufac-

ture of acrylamide monomer. It should be explained that acrylamide is a contact poison, that the effects are not noticed immediately because acrylamide damages the nervous system only after a prolonged exposure, that the effects of acrylamide are cumulative, and that brain and nerve damage are the known results of exposure. In regard to hygiene, dermal contact should be prevented by protective clothing in the form of long polyvinyl gloves, light washable overalls, a head covering, a face shield and a mask to prevent inhalation of airborne dust. Good washing facilities should be provided, smoking or eating on the job forbidden, and protective clothing changed regularly. Individuals exposed to acrylamide monomer should be encouraged to report any unexplained change in health status such as skin peeling, excessive tiredness, "pins and needles" sensations, numbness, or sweating in the hands or feet. Warning labels on bags of monomer should contain a clear message that acrylamide is a contact poison and that repetitive exposure might result in brain and nerve damage.

In addition to education and hygiene, a simple test is needed to check the health of workers daily exposed to acrylamide monomer. Unfortunately, monitoring urine would not provide information on the amount of protein-bound acrylamide accumulating in the body (19). A blood test might be more informative, since acrylamide is strongly bound to hemoglobin (18), but such a test would be time-consuming, expensive, and unlikely to be tolerated by factory workers. Clinical measurements of nerve conduction are not reliable indicators of early peripheral nerve disease of the dying-back type, since the initial changes in the nerve affect only a few fibers and the predominant change is at the distal tip. A promising area which is presently under consideration springs from the observation that Pacinian corpuscles are one of the most vulnerable structures in intoxicated cats (28). If it is possible to demonstrate that the human corpuscle is likely to behave in the same way, it may be feasible to develop a sensitive, practical and economic test based on periodic examination of palmar sensibility.

Control Measures

The singular importance of acrylamide to the polymer industry is evident from the fact

that in North America alone, annual production is estimated to be 50 million pounds and to be increasing rapidly. Perhaps no other potentially neurotoxic substance is produced in such vast quantities or enjoys the importance that acrylamide has assumed in the production of commercially useful polymers. Because of the neurotoxic potential of acrylamide, it is essential that its manufacture and its use conform to realistic safety standards which will prevent dangerous exposure either to factory workers or to the populace.

At the present time, it is recommended that factory workers should not be daily exposed to more than 0.5 mg/kg acrylamide monomer and that air levels should not exceed 0.3 mg/m³ (2,41). Since cases of acrylamide neuropathy still occur in factory workers, either these permitted levels are too high, or precautions taken to reduce exposure to an acceptable level are inadequate.

The second area for some concern lies in the present practice permitting some residual contamination of polymers by the neurotoxic acrylamide monomer. Up to 2% residual monomer is considered acceptable for some industrial applications of polyacrylamide, as in the flocculation of ore slimes (14). The Food and Drug Administration has established a maximum level of 0.05% residual acrylamide monomer for polymers used in paper and paperboard in contact with foodstuffs. Similar levels are considered satisfactory for the polymers used in the clarification of potable water and cane-sugar juice. These levels have been calculated from data obtained in a clinical study of primate acrylamide intoxication conducted ten years ago (2). Because of recent data which have underlined the danger of prolonged low level exposure, the possibility of irreversible central nervous system effects and the identification of peripheral nerve damage before clinical symptoms appear, it seems important to confirm that present regulations are adequate.

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