A Review of Acrylamide Neurotoxicity
Part I. Properties, Uses and Human Exposure

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SUMMARY: *Two factors have stimulated the present intense investigation of acrylamide neurotoxicity. These are the health hazard accompanying the vast and increasing industrial production of acrylamide, and the promise of illuminating the mechanism of dying-back disease in the human nervous system by employing acrylamide as an experimental tool. The present paper discusses the industrial uses of acrylamide, its regulation, and the prevention, detection and clinico-pathologic features of human intoxication. Bearing on the cumulative nature of acrylamide neurotoxicity, separate sections review the chemistry, biochemistry, toxicology and metabolic fate of acrylamide. Clinical, electrophysiological and morphologic data on acute and chronic acrylamide intoxication of experimental animals, and possible etiologies of nervous system damage, are considered in detail in a companion paper (P. S. Spencer and H. H. Schaumburg, Canadian Journal of Neurological Sciences, 1:151, 1974).*

RÉSUMÉ: *Deux facteurs ont encouragé l'actuelle recherche intensive effectuée sur la neurotoxicité de l'acrylamide. Le premier est le risque que représente pour la santé, la grande et toujours croissante production industrielle d'acrylamide; le second est l'espoir d'élucider le mécanisme de la maladie "dying-back" dans le système nerveux humain, par l'emploi de l'acrylamide comme outil expérimental. Cet article explique les usages industriels de l'acrylamide, sa réglementation, ainsi que la prévention, le dépistage et les symptômes clinico-pathologiques de l'intoxication humaine. S'appuyant sur le caractère cumulatif de la neurotoxicité de l'acrylamide, différents paragraphes passent en revue la chimie, la biochimie, la toxicologie et la destinée métabolique de l'acrylamide. Dans un article complémentaire (Spencer et Schaumburg, Canadian Journal of Neurological Sciences, 1:151, 1974) sont exposés en détail les données cliniques, électrophysiologiques et morphologiques de l'intoxication chronique aigüe par l'acrylamide chez des animaux de laboratoire, ainsi que les causes possibles de la détérioration du système nerveux.*

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INTRODUCTION

The neurotoxicity of acrylamide was recognized in the early 1950's during toxicologic studies (Hazleton quoted by Kuperman, 1957) prompted by the advent of large-scale production of the chemical for the polymer industry. Within five months of commencing manufacture of acrylamide, several factory workers developed a peripheral neuropathy strikingly similar to neurologic signs previously noted in animals chronically intoxicated with acrylamide (Golz quoted by Fassett, 1962 and Fullerton and Barnes, 1966; Kuperman, 1957). In recent years, as the production of acrylamide has mushroomed, its neurotoxic potency has continued to be an industrial health hazard as well as a potential hazard to users of derivative products.

In research medicine, its neurotoxicity has been used to produce an animal model of human nervous system disease whose pathologic hallmark is distal axonal degeneration. Despite the many experimental studies utilizing acrylamide, neither the site of toxic action, nor the precise mechanism of nervous system damage is known. It is our intention here to review the properties of acrylamide and the data relating to its human neurotoxicity. A companion paper discusses the effects of acrylamide on experimental animals and possible mechanisms of nervous system damage (Spencer & Schaumburg, 1974).

CHEMISTRY

Acrylamide is a white crystalline solid with a molecular weight of 71.08, a melting point of 84.5° C. and a tendency to sublime, even at room

temperature (Bikales and Kolodny, 1963). It is highly soluble both in water (2.15 g/ml at 30° C.) and in polar organic solvents (eg., 0.86 g/ml in ethanol at 30° C.) and reacts with hydroxy, amino and sulfhydryl compounds (Bikales and Kolodny, 1963; Bikales, 1970; Cavins and Friedman, 1967a, 1967b; Druckrey et al. 1953; Hashimoto and Aldridge, 1970). Acrylamide is stable in solution and does not polymerize spontaneously.

The acrylamide molecule consists of two principal functional groups: an amide group and a vinyl group that is conjugated with it:

$$CH_2{=}CH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2.$$
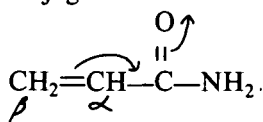
Because of the electron withdrawing character of the amide group, acrylamide readily undergoes addition reactions at the β-position with compounds having active hydrogen atoms, such as molecules containing thiols, hydroxy and amino groups. This type of reaction generally requires a basic catalyst and is referred to as carbamoylethylation (Bikales and Kolodny, 1963; Bikales, 1970). Significantly, thiols and especially amino groups are very reactive in the absence of catalyst. The double bond can also readily undergo vinyl-type polymerization to form polyacrylamide:

$$-(CH_2{-}CH)_{\overline{x}}$$
$$| $$
$$CONH_2$$
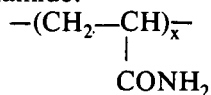
USES

The major use of acrylamide is as a vinyl monomer in the production of high molecular polymers. Available since the early 1950's, consumption of acrylamide polymers has increased dramatically and in 1972, an estimated 35 million pounds were used for this purpose in the U.S.A. alone (Anon., 1971, Bikales, 1973). Three manufacturers in North America produce over 50 million pounds per year of the neurotoxic acrylamide monomer, and levels are increasing rapidly (Bikales, 1974). The major reason for this expansion in the production of acrylamide is the increasing application of acrylamide polymers commercially and industrially. Acrylamide polymers were first used as flocculants and to increase dry strength in paper and board. In recent years, new polymers have been developed, each with specific applications (American Cyanamid, Dow and Nalco Co. patents). These include polyacrylamides for the clarification and treatment of municipal and industrial effluents (Flock and Rausch, 1973; Restaino, 1970), potable water and foods (Bikales, 1973). Acrylamide polymers are used to stimulate oil-well production by fracturing and flooding oil-bearing strata and forcing the oil to the surface (MacWilliams et al., 1973). They are employed as flocculants in the production of ores, coal, and in the metal finishing industry (Sussman and Chun-Chin Wang, 1973). Acrylamide polymers will break oil-in-water emulsions, dissipate fog and stabilize soil. Acrylamide is widely used as a grouting agent; it is pumped into dirt, clay and stone walls of excavations in a liquid state together with a crosslinking agent and a catalyst, where it polymerizes to produce a watertight shield (Auld and Bedwell, 1967; Bikales and Kolodny, 1963). Acrylamide copolymers have been recommended for use in swimming pools and cooling towers to inhibit algae and bacterial growth (Hoover, 1970). In research biology and medicine, biochemists employ acrylamide to produce polyacrylamide gels for electrophoresis. Other important applications are in coatings for metals (Bikales and Kolodny, 1963), in adhesives and binders, and in photography (Bikales, 1974).

For industrial production of acrylamide polymers, polymerization of 8-30% acrylamide solutions, adjusted to pH 3-6, is initiated by low (0.005-1%) concentrations of free radicals of the redox type (Bikales, 1973). Examples of initiators are sodium bromate/sodium sulfite, and potassium persulfate/sodium metabisulfite. One of the components of the chosen redox system is dissolved in the reactor vessel together with the monomer; the other component, e.g., the reducing agent, is then added gradually to control the rate of polymerization and to prevent the temperature from becoming excessive. Metal ions such as Cu^{++} and Fe^{++} frequently are used as cocatalysts. Industrial processes utilize free-radical methods of polymerization to produce a variety of polymers differing in molecular weights (from ca. 200,000 to ca. 10,000,000) and composition. By far the greatest current interest is in the production of polymers having molecular weights in the order of five million. This requires very low concentrations of initiators and the absence of oxygen and other interfering substances. A high purity of acrylamide monomer is therefore essential, particularly with respect to traces of metal. Commercial grades of acrylamide with less than 10 ppm of iron are satisfactory and can be used without further purification (Bikales, 1973).

Acrylamides possess antitumor properties and have been considered in the search for cancer therapeutics (Ismailova, 1966; Ismailova et al., 1966; Tomcufcik et al., 1961).

REGULATION

Although the pure acrylamide polymer is non-toxic (Kuperman, 1957; Rakhmanina, 1966; Regelson, 1973; but see Lazareva, 1967), the present practice is to permit some 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 (Bikales, 1973). The Food and Drug Administration has established a maximum level of 0.05% residual acrylamide for acrylamide polymers used in paper or paperboard in contact with foodstuffs. Similar residual levels of acrylamide monomer are considered satisfactory for the clarification of potable water and cane-sugar juice. The Environmental Protection Agency has established strict toxicological test procedures that must be met before a coagulant can be used in potable

water. These involve determination of residual acrylamide, acute toxicity and metabolism studies, as well as chronic toxicity, carcinogenecity, teratogenicity and mutagenicity studies. Levels of acrylamide polymer below 3 mg/1 do not impart an aftertaste (Rakhmanina, 1966). Because of the cumulative nature of acrylamide, McCollister et al. (1964) stated the populace should not be exposed to daily levels in excess of 0.0005 mg/kg.

TOXICOLOGY

Since the molecular charge distribution is a factor in determining pharmacologic behavior, the reactivity of acrylamide in vivo is difficult to predict (Kuperman, 1957). Compounds with minor structural variations of the acrylamide molecule have been tested in animals to determine the neurotoxic moiety of acrylamide. These acrylamide analogues have altered chemical characteristics at the vinyl and/or the carbonyl groups and, as a consequence, the neurotoxic potency either is abolished or reduced. Many saturated or vinyl-substituted analogues retaining the amide function (propionamide, crotonamide, 3-butenamide and benzamide) and analogues with the vinyl group intact, but with changes in the simple amide function (2-methylacrylamide, N-ethylacrylamide, N,N'-diethylacrylamide, N-butylacrylamide, N-tert-butylacrylamide, N-tertoctylacrylamide, N,N'-methylenebisacrylamide) are less or non-neurotoxic (American Cyanamid Co., 1954; American Cyanamid, quoted by Kuperman, 1957; Barnes, 1970; Hazleton, quoted by Kuperman, 1957; Shaffer, quoted by Fassett 1963). Kuperman (1957) indicated that methacrylamide $(CH_2=CCH_3 CONH_2)$ was fifteen times less neurotoxic than acrylamide, but (Fassett, 1963) stated this substance is not neurotoxic. Kuperman (1957) also specified that N (2-hydroxyethyl) acrylamide was ten times less toxic than acrylamide and Fassett reported the slight neurotoxic property of both N,N¹-dimethylacrylamide and N-isopropylacrylamide. Barnes

(1970) indicated N-methylacrylamide $(CH_2=CHCONHCH_3)$ produced a slight neuropathy after chronic administration. It now seems established that purified N-hydroxymethylacrylamide, also known as N-methylolacrylamide, $(CH_2=CHCONHCH_2OH)$ is about one fifth as potent as acrylamide (Edwards, 1973; Fullerton and Barnes, 1966; Kuperman, 1957) and is able to predispose animals to the neurotoxic effects of acrylamide (Hashimoto and Aldridge, 1970; Yocum and Nyquist, 1973). Other related substances (furylfuramide, 2-methylglutarimide, senecoic acid amide and many N,N¹-dimethylamides) produce no neurotoxic effects (Barnes, 1970; Kuperman, 1957; Miyaji, 1971; Wiles and Narcisse, 1971), although repetitive dosing of animals with ethionamide or prothionamide may lead to a peripheral neuropathy similar to that produced by isoniazid intoxication (Leggat, 1962; Poole and Schneeweiss, 1961; Tala and Tevola, 1969).

METABOLIC FATE

Early experiments on the fate of labeled acrylamide $(CH_2=CHC^{14}ONH_2)$ in vivo found the substance widely distributed in the body, with a tendency for the most vascular organs to contain the highest levels (Ribelin, 1964; West, 1959). Tarusov and co-workers (1966a, 1966b) reported label in the brain, nerves and other organs of tadpoles after total body immersion in a solution of labeled acrylamide. More recently Hashimoto and Aldridge (1970) have demonstrated some acrylamide is freely distributed in vivo but the majority is bound to tissue and circulating protein, especially hemoglobin. Highest levels of free/soluble and protein-bound label were recorded from whole blood, with progressively less label in kidney, liver, brain, spinal cord and sciatic nerve one day after a single injection of $(1-^{14}C)$-acrylamide; by 14 days, the majority of free/soluble label had disappeared, but the protein-bound label remained at approximately 25% of the first day's level, except in whole blood, which

was 100%. N-hydroxymethylacrylamide, a substance which is about one fifth as neurotoxic as acrylamide (Edwards, 1973), behaved similarly in vivo except that the free/soluble label was lost from all tissues except kidney after only 4 days. The distribution of radioactivity in subcellular fractions of brain 24 hours after the administration of labeled acrylamide or labeled N-hydroxymetylacrylamide indicated all fractions were labeled. The specific activity of the protein was very similar in each fraction (Hashimoto and Aldridge, 1970). Ando and Hashimoto (1972) examined the distribution of radioactive label in the sciatic nerve and brain of mice made ataxic by repeated dosing with (^{14}C)-acrylamide. Activity in the distal half of the sciatic nerve was 2.5 and 4 times higher than in the proximal half and the brain respectively, an important finding in view of the distal distribution of peripheral nerve damage (Spencer and Schaumburg, 1974).

The amount of acrylamide excreted in urine may be estimated by the standard iodine double bond determination, by polarography (American Cyanamid Co., 1956; Kuperman, 1957), spectrophotometrically using 4-dimethylaminocinnamaldehyde (Mattocks, 1968) or by gas chromatography (Croll, 1973). Data on excretion rates of labeled acrylamide are somewhat variable: 40%-65% of the label is excreted in 24 hours and 60%-85% by 3-4 days (Ziegler, 1969) although, as indicated above, considerable amounts of radioactivity may be present 14 days after a single dose (Hashimoto and Aldridge, 1970). Two-thirds of the label is excreted via the urine, very small amounts in the feces after oral dosing, and some in the exhaled air, suggesting there is slight metabolism in vivo (Hashimoto and Aldridge, 1970; Kuperman, 1957; West, 1959). Kaplan et al. (1973) suggested acrylamide metabolism might occur in the liver but this was earlier denied by Kuperman (1957). Ziegler (1969) stated that 80%-89% of the label in urine was due to metabolites, in agreement with the observations of

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Mattocks (quoted by Hopkins, 1968). On the other hand, recent studies have indicated acrylamide is excreted unchanged (Edwards, 1972; Hashimoto, 1972; Hashimoto and Ando, 1971).

BIOCHEMISTRY

The precise biochemical lesion produced by acrylamide is unknown but its reactivity with nervous system proteins seems established (Hashimoto and Ando, 1973). That acrylamide reacts with proteins was first shown by Druckrey and associates (1953). They demonstrated that mixtures containing acrylamide and various protein brines, or human serum, hardened into solid, clear gels within short periods of time. The speed of the process was both concentration and temperature dependent, and was influenced by the nature of the protein; mixtures which hardened rapidly contained elongate or filamentous proteins. This phenomenon was confirmed by Kuperman (1957), who demonstrated that mixtures of acrylamide (300-600 mg/1) and whole human blood hardened, while acrylamide analogues, including methacrylamide, had little or no effect on the viscosity of blood. Kuperman stated these effects were unlikely to result from polymerization of acrylamide. Gelation of acrylamide, presumably by polymerization, is well known in industry (Bikales, 1970).

Experiments have demonstrated that acrylamide, in common with other conjugated unsaturated compounds, reacts with proteins and non-protein thiols (Cavins and Friedman, 1967a, 1967b; Hashimoto quoted by Barnes, 1969a; Hashimoto and Aldridge, 1970). Acrylamide is especially reactive with cysteine sulfhydryls in protein producing S-carboxyethyl cysteine after hydrolysis (Hashimoto and Aldridge, 1970). Acrylamide reduces glutathione levels in the spinal cord (Hashimoto, quoted by Barnes, 1969a), brain, liver and blood (Hashimoto, quoted by Hopkins, 1968) but the significance of these findings is uncertain since acryl-amide and N-hydroxymethylacrylamide react identically with glutathione in vitro, despite the considerable difference in neurotoxic potency of these two compounds (Edwards, 1973).

Amino acid incorporation into proteins of the nervous system in vitro and in vivo is altered after the administration of acrylamide. Hashimoto and Ando (1971, 1973) demonstrated that incorporation in vitro both of ^{14}C-lysine and ^{35}S-methionine into cerebral cortex and liver was unchanged, while in the spinal cord, incorporation was normal until the rats became paralyzed when the amino acid incorporation increased, reaching a maximum after acrylamide was withdrawn. Autoradiographically, a large amount of label was visible in anterior horn cells suggesting these were largely responsible for the changes in amino acid uptake. By contrast Ashbury and colleagues (1973) have demonstrated a decreased uptake of labelled leucine by anterior horn cells in vivo. In Schwann cells of sciatic nerve Hashimoto and Ando (1973) found incorporation of lysine was suppressed at an early stage but increased later, while methionine incorporation remained normal.

Amounts of RNA and DNA in nervous tissues of rats are not affected by acrylamide dosing but ^{3}H-uridine incorporation into sciatic nerve increases two weeks after continuous feeding with acrylamide (Ando and Hashimoto, 1971). Acrylamide does not interfere with oxidative phosphorylation (Hashimoto and Aldridge, 1970), and Wilke's suggestion that tissue damage is caused by acrylamide polymerization and swelling (Wilke, 1952, 1953; Wilke and Gensel, 1951, 1952) has not been demonstrated.

CUMULATIVE NATURE OF ACRYLAMIDE NEUROTOXICITY

Kuperman (1957, 1958) first showed that the time of onset of neurological signs in intoxicated animals depended on the accumu-lated dose of acrylamide, and that by whatever route the chemical was administered, clinical signs appeared when the animals had received an average of 102 mg/kg, whether this was given over a period of a few days or several months. Although several factors determine the onset of clinical signs, the cumulative action of acrylamide has been stressed by many other authors (Anon, 1967a; Fullerton and Barnes, 1966; Hamblin, 1956; Kaplan et al., 1973; McCollister et al., 1964).

Several investigators have attempted to account for the insidious neurotoxicity of acrylamide. Kuperman (1957) suggested his experimental evidence indicated that the cumulative action of acrylamide was a result of the persistence of pharmacologic effects of each dose and not through an accumulation of the neurotoxin. In his view, acrylamide probably inactivated enzyme systems important for normal neural function. To explain the severe, but short-lasting effects of large doses, Kuperman suggested acrylamide inactivated diffuse and rapidly regenerated enzyme systems. To account for the effects of chronic intoxication, he postulated that acrylamide destroyed enzymes with a limited distribution and which were only replenished slowly. Hashimoto and Aldridge (1970) stated that acrylamide probably reacts with some component of nervous tissue, the product of the reaction persisting long enough for subsequent doses to increase the concentration of the modified component. Finally, on the basis of structural similarities between two acrylamide molecules and nicotinamide, Kaplan et al. (1973) suggested acrylamide might act as a nicotinamide antagonist, competing for sites necessary for the production of NAD and NADP. They further suggested the great sensitivity of cats to intoxication with acrylamide might be explained by their inability to convert tryptophan to nicotinamide, making them less tolerant of any interference with their pyridine nucleotide coenzyme metabolism.

HUMAN TOXICITY

Acrylamide intoxication in man first was recognized in workers engaged in the industrial manufacture of acrylamide from acrylonitrile in 1954 (Golz, quoted by Fassett, 1962; Kuperman, 1967). Several cases of acrylamide poisoning through industrial exposure have appeared since these initial victims. Human intoxication still occurs in the U.S.A. despite the implementation of extensive precautions in industry to reduce exposure (Pleasure, 1973; Shaffer, 1973). In Japan, a total of 28 cases of acrylamide neuropathy have been reported; two patients were studied clinically by Masuoka (1965); examination of ten patients was conducted by Fujita et al. (1960), and fifteen by Takahashi and colleagues (1971), and one was reported anonymously (Anon., 1967b). Morviller (1969), Graveleau and co-workers (1970) and Cavigneaux and Cabasson (1972) have reported a total of six cases in France and a single patient was seen in Canada (Auld and Bedwell, 1967). Garland and Patterson (1967) examined six English workers with varying degrees of acrylamide neuropathy, three of whom were subsequently tested electrophysiologically (Fullerton, 1969a, 1969b, 1970).

The mode of acrylamide intoxication of factory workers has not been clearly established although local dermal contact seems more likely than inhalation (Garland and Patterson, 1967; Kuperman, 1957). This was concluded from an analysis of atmospheric contamination by acrylamide undertaken at various sites of plant operations. Only trace quantities of acrylamide were found, such that the total amount inhaled by workers was approximately 1.8 mg/kg over a five-month period, the time lapse between onset of acrylamide manufacture and the first patient symptomatology. This exposure to acrylamide in the air was considerably below the amounts needed to produce neurologic signs in rats (360 mg/kg) or dogs (20-25 mg/kg) by inhalation of acrylamide (Hazleton, quoted by Kuperman, 1967). McCollister et al (1964) found that ac-

rylamide could enter the body in toxic amounts solely by dermal contact. That such contact occurred in some workers is established. For example, the patient seen by Auld and Bedwell (1967) was employed to load hoppers with a 10% solution of acrylamide and then add the catalyst and activator (dimethylaminopropionitrile) for polymerization. During this procedure, the patient acknowledged that the acrylamide solution frequently had splashed on his unprotected hands, forearms and face.

The earliest and most consistent signs of local acrylamide contact are erythema and peeling of the palms. This may be caused by solutions as dilute as 1% (Fassett, 1963). This contact dermatitis precedes neurologic symptoms by several weeks. Shortly after evidence of contact dermatitis, workers may notice excessive fatigue, weight loss and somnolence (Garland and Patterson, 1967). The neurologic picture of acrylamide intoxication appears after chronic exposure. The syndrome consists of a slowly progressive, symmetrical, peripheral neuropathy in a distal distribution, with some evidence of central nervous system disturbance (Garland and Patterson, 1967). In most reports, patients present with complaints of unsteadiness, muscle weakness and paresthesia, with numbness in the hands, and/or feet. Frequently, sensory symptoms precede and predominate over motor signs and sympathetic nervous system involvement often complicates the picture (Takahashi et al., 1971). As emphasized by Auld and Bedwell (1967), patients display cold, blue hands and feet which sweat excessively. Fine movements of the hand, such as writing and shaving, become noticeably difficult and there may be impaired temperature sensation. On examination, tendon reflexes in the arms and legs usually are sluggish or absent, and joint position sense may be impaired. All the patients examined by Takahashi and co-workers (1971) displayed superficial sensation or vibration sense impairment. Weakness in the

hands and legs is an early motor sign. There may be considerable loss of power with prominent atrophy of the small muscles of the hands. Speech is sometimes slurred and bladder incontinence has been reported. Signs suggestive of central nervous system involvement are somnolence, past-pointing, tremor, ataxic gait, vertigo, and an occasional mild organic mental syndrome (Garland and Patterson, 1967; Fujita et al., 1960; Pleasure, 1973). Abnormal EEG recordings have also been described (Takahashi et al., 1971).

If patients are removed from the source of intoxication, signs of peripheral neuropathy gradually disappear; in less severely poisoned individuals, complete recovery may occur within 2-12 months (Garland and Patterson, 1967). Tendon reflexes and superficial sensation return last (Fullerton, 1969a). Animal experiments suggest re-exposure to acrylamide after recovery may precipitate a more rapid onset of symptoms (Stockinger, 1956).

Nerve conduction studies and electromyography have been performed on several patients with acrylamide neuropathy both before (Fujita et al., 1960; Takahashi et al., 1971) and during recovery (Fullerton, 1969a, 1970). Summarizing the results, there is a tendency for abnormalities to be confined to the distal regions of nerves, although proximal conduction times may be increased above normal. Abnormalities are found in all extremities. Maximal motor nerve conduction velocity usually is normal, but the muscle response to nerve stimulation is dispersed and potentials with markedly prolonged distal latencies are found. Sensory nerve conduction appears to be more affected than motor conduction. In the distal parts of the tibial or median nerves, the amplitude of the sensory action potential may be reduced or absent.

Sural nerve biopsies from three patients recovering from acrylamide neuropathy were examined by Fullerton (1969a). Density of 2-9 μm nerve fibers was in the control range, but there was a marked reduction in the large (10-16μm) fiber
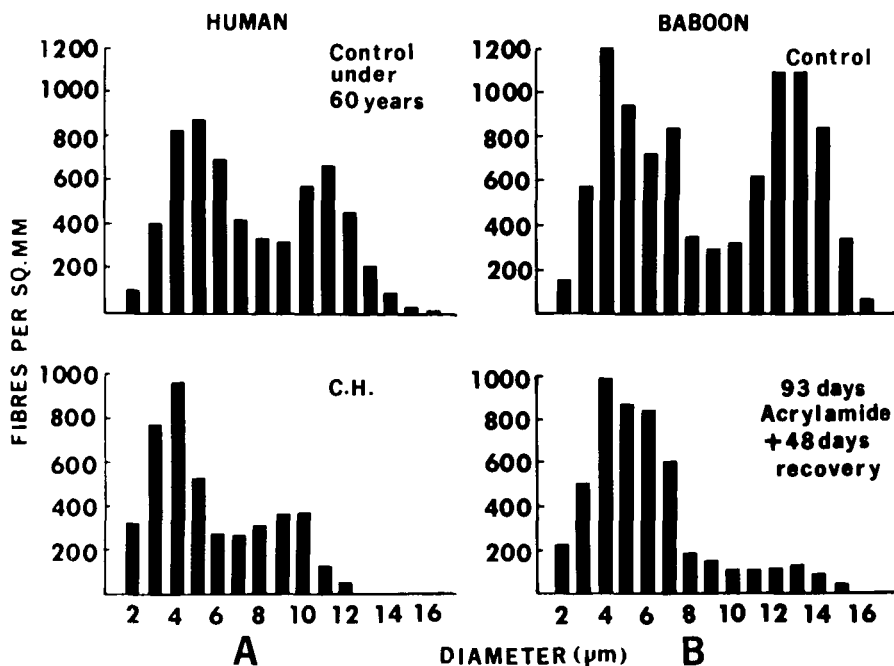
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Figure 1. A (left). Histogram of nerve fiber diameter in a normal adult human sural nerve (upper) and in the sural nerve of a patient recovering from acrylamide neuropathy (lower). (Figure 6, Fullerton, 1969a, reproduced by permission).
B (right). Histogram of nerve fiber diameter in the sural nerve of a control baboon (upper) and in a baboon recovering from acrylamide neuropathy (lower). (Part figure 47, Hopkins, 1968, and figure 6, Hopkins and Gilliatt, 1971; reproduced by permission).

density of one patient (Fig. 1A). Hopkins (1968) and Hopkins and Gilliatt (1971) subsequently demonstrated a similar pattern of fiber loss in baboons recovering from acrylamide neuropathy (Fig. 1B). In single, isolated nerve fibers, there was no abnormal incidence of segmental remyelination, but regenerating fibers, recognized by lengths of many uniformly short internodes with respect to their fiber diameter, were prominent in the sural nerve of one patient biopsied by Fullerton. Since regeneration was well advanced two-and-half months after the patient had ceased employment, it seemed likely to Fullerton that regeneration had occurred during exposure and even prior to onset of symptoms.

PREVENTION AND EARLY DETECTION OF HUMAN INTOXICATION

To maintain the health of workers engaged both in the manufacture and in the use of acrylamide, a simple test is needed to prevent an exposure resulting in clinical impairment. Unfortunately, monitoring urine levels would not provide information on the amount of protein-bound acrylamide accumulating in the body. By contrast, since a considerable amount of acrylamide is strongly bound to hemoglobin (Hashimoto and Aldridge, 1970), further exploration of this phenomenon might result in an informative blood test. Another promising area for investigation centers on the observation that some Pacinian corpuscle axons degenerate before onset of clinical signs in intoxicated cats (Schaumburg et al., 1974). Since Pacinian corpuscles are mechanoreceptors, it might be feasible to develop a sensitive, practical and economic test based on periodic examination of palmar sensibility.

At the present time, it is recommended that factory workers should not be daily exposed to more than 0.05 mg/kg of acrylamide (McCollister et al., 1964) and that air levels should not exceed 0.3 mg/m^3 (Cavigneaux and Cabasson, 1972). Since cases of acrylamide neuropathy still occur in factory workers (Pleasure, 1973; Schaffer, 1973), either these permitted levels are too high or precautions taken to reduce exposure of factory workers to an acceptable level are inadequate.

Garland and Patterson (1967) stated that, theoretically, the industrial use of acrylamide was a relatively easy hazard to contain. They suggested dermal contact should be prevented by protective clothing in the form of long poly (vinyl chloride) gloves (but see Pegum and Medhurst, 1971), light washable overalls, head covering, a face shield and a mask to prevent inhalation of atmospheric acrylamide. Good washing facilities should be provided, smoking or eating on the job forbidden, and protective clothing changed regularly. Above all, the dangers of chronic exposure to acrylamide should be explained to factory workers and warning labels on bags containing acrylamide written in simple language. On a practical level, however, Garland and Patterson (1967) recognized that managerial enforcement of precautions was difficult. For example, they saw a supervisor dip his bare hand into a solution of polymerizing acrylamide to see how gelling was proceeding, despite his knowledge of mandatory instructions to carry out the process without skin contact.

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