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REPORT

INTERNATIONAL CONFERENCE ON PERIPHERAL NERVE TOXICITY

(12–13 June, 1993, Kanazawa, Japan)

The International Conference on Peripheral Nerve Toxicity was attended by 135 persons. Italy, Saudi Arabia, the Netherlands and China were represented by one delegate from each country, the United States of America and United Kingdom by two delegates, Tiwan and Korea by three. Other participants represented various university centres of Japan.

During all Conference sessions 25 papers were presented and 24 posters during two poster sessions.

The programme of the Conference included five sessions devoted to the following main topics: 1. Acrylamide, 2. Pesticides, 3. Drugs and some other chemical substances, 4. Organic solvents and ethylene oxide, and 5. Metals.

The Conference was opened by its Chairman, Professor *K. Hashimoto* (Kanazawa University). The opening address was followed by a special lecture on the effect of organophosphate compounds on the development of delayed polyneuropathy, given by *M. Lotti* (University of Padva, Italy). This issue was related with and idea of "neuropathy target esterase" (NTE) which is thought to be an important factor in the developing of delayed polyneuropathy.

NTE inhibitors are ranked in two groups:

A. phosphates, phosphonates and phosphoroamidates which inhibit 70% of NTE, and

B. phosphinates, sulphonates and carbamates which inhibit almost all NTE.

Compounds from group B when given before compounds of group A protect peripheral nerves.

The author presents an opinion that compounds of group A act as agonists and compounds of group B as antagonists of NTE enzyme. There exist substances of intermediate efficacy on NTE such as methamidophos (0.5-dimethylphosphoroamidothioate).

Session devoted to peripheral effects of acrylamide was started with a review lecture given by *G.J. Harry* (USA). He reported that cellular macromolecules are sythesized in the neuronal cell body and transported in a continuous fashion to their final destination in the neuronal processes. Disturbances in the supply of axons with these molecules can have a detrimental effect on the structure and function of the axon. Toxicants can produce disturbances in macromolecular transport, they can also influence the energy metabolism. The author presented models of toxicant-induced alterations in axonal transport and significance of these alterations in the pathogenesis of peripheral neuropathies.

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This was followed by four original findings on acrylamide peripheral neuropathy. *H. Igisu* (Japan) indicated similarities between acrylamide neuropathy and giant axonal neurpathy. The evidence was presented that in the latter disease entity not only axons but also fibroblasts show aggregation of intermediate filaments. Similar abnormalities can be induced in experimental studies on exposing normal fibroblasts to acrylamide. Giant axonal neuropathy is, however, a genetic disease. A certain analogy can be observed with the Krabbe diseases whose pathogenic mechanism can be explained by a genetically determined defficiency of beta-galactosidase-galactysol-ceramide. The author postulates that the same enzyme can participate in the pathogenesis of acrylamide neuropathy. The Krabbe disease is conditioned by a genetic defficiency of this enzyme and is regarded as storage disease. In the acrylamide-included syndrome, symptoms of storage disease may result from a toxic blockade of the enzyme.

P.M. Edwards and *W. H. Gispen* (The Natherlands) presented the contrasting effects of acrylamide and neurotrophic melanocortins. Melanocortins are peptides which accelerate recovery of peripheral nerve function following mechanical injury. The peptides stimulate the sprouting response and improve the nerve conduction velocity and thus, their effect is opposite to that of acrylamide. The authors indicated a physiological connection between the two substances significant in the metabolizm and neurofilament turnover.

M. Matsuoka and *H. Igisu* (Japan) compared effects of ischemia on brain energy metabolites in mice intoxicated with acrylamide. The authors based their studies on previously published findings that acrylamide inhibits glycolytic enzymes. They found that acrylamide inhibits the activity of creatine kinase. The concentrations of phosphocreatine, ATP, ADP, AMP, glucose and lactate in the whole brain in mice intoxicated with acrylamide and in the controls were investigated. Differences were not significant and the same experiment performed on a mouse under ischemia revealed similar changes in concentrations in both groups of animals. The only difference was the lower pyruvate in the brain of acrylamide-intoxicated mice.

K. Saita et al. (Japan) discussed the effect of 4-methylcatechol on acrylamide neurpathy of rats. It was indicated in histological and neurophysiological examinations that 4-methylcatechol improves neurological, electrophysiological and biochemical deficits in rats exposed to acrylamide.

Four posters on toxic effect of acrylamide on peripheral nerves supplemented this session.

Tanaka H. et al. (Japan) studied the regeneration of the stump of a transected mouse peripheral nerve on a thin plastic film by comparing acrylamide, N-isopropylacrlylamide, N-methylacrylamide and N,N-methylene-bis-acrylamide. Stumps treated with N,N-methylene-bis-acrylamide regenerated at the same rate as in controls while other acrylamide compunds disturbed the process of regeneration.

K. Torigoe et al. (Japan) also studied regeneration of neurites treated with acrylamide. They presume that regenerating disturbances (in the initial period higher growth and then declined) depend on a change in the amount of neurofilaments within axon. The authors examined, using a transmission electron microscope, the relationship between the amounts of neurofilaments and neurotubles. They indicated that the number of neurofilaments progressively increased until they were piled together in a longitudinal direction to form a band beneath the axolemma.

The same team presented the response of Schwann cells to axotomy in acrylamide neuropathy. They revealed that Schwann cells are not directly involved in the growth of regenarating axons.

K. Hashimoto et al. (Japan) dealt with an automated quantitaive mesurement of motor activity in mice after repeated administration of acrylamide. They investigated neurotoxicity and noticed soon after administration of acrylamide the vertical movements of mice. They also performed comparative studies using carbon tetrachloride and ethanol.

The second session was focussed on toxic effects of pesticides. The session was chaired by Professor *C.W. Cha* (Korea) and the review lecture was presented by *W.N. Aldrige* (United Kingdom). He concentrated his attention on the toxicology of pyrethroids and pointed out to the occurrence of hyperesthesia in humans exposed to pyrethroids. This could suggest demage of peripheral nerves.

During the course of this session three original findings were presented. The authors from Beijing (China) – *X. Zhang* et al. discussed the toxic effects of parathion on biomembrane. Human erythrocytes were used as a study model and the effect of parathion on the Ca^{2+} uptake by inside-out vesicle was indicated. The same effect on the calcium metabolism was indicated in synaptosome membranes.

S.A. Soliman et al. (Saudi Arabia) screened workers occupationally exposed to organophosphorus pesticides in view of peripheral neuropathy. In the group of workers exposed to organophosphorus lymphocyte neuropathy target esterase activity was significantly lower than in workers from other plants. Tactile thresholds were also investigated and it was indicated that their levels were lowered in workers involved in production of organophosphorus compounds. The authors suggest that the tactile sensitivity testing may provide a useful method for detection of peripheral neurpathy in workers occupationally exposed to pesticides.

H. Kinebuchi et al. (Japan) presented the study on delayed neuropathy caused by organophosphates in Japanese quails. They used subcutaneous injection as the route of triortho tolyl phosphate administration. Acute demage of nerves up to severe paralysis was observed when relatively high doses (250, 500 or 750 mg/kg body weight per day) were administered for 8 days.

Two posters were also devoted to effects of organophosphates on peripheral nerves: *N. Konno* (Japan) – Binding sites for [^{3}H] diisopropylfluorophosphate on membranes from chicken nervous tussues, and *T. Yamauchi* et al. – Intrasynaptosomal free Ca^{2+} of hens affected by organophosphorus induced neuropathy. It was indicated that verapamil, a typical Ca^{2+} channel blocker, generates the development of peripheral neuropathy *in vivo*. Investigations *in vitro* did not show significant effect of several different organophosphates on the level of Ca^{2+}.

Toxic effect of drugs and other chemicals was the topic of the third session chaired by Professor *A. Ohnishi* (Japan). Five original presentations and four posters were included in the programme of this session.

T. Hashimoto et al. (Japan) presented neurotoxic effects of cisplatin in 35 females with gynecologic neoplasms. In six of them parasthesia was observed, in one decrease of superficial sensation, in eight decrease of vibration sensation and in three decrease or absence of ankle jerk. There was no correlation between the total dose and neurological symptoms. However, it was found that the median of the total doses at the onset of the symptoms ranged between 150 and 200 mg/m^2.

Chau-Hsiung Pan and *Shun -Sheng Chen* (Taiwan) shared their observations on disturbances of the central nervous system and peripheral nerves in amphetamine abusers. Electroencephalography did not reveal more significant disorders, nevertheless, impairment of conduction in peripheral nerves was noted.

T. Yamamoto, A. Ohnishi and *Y. Murai* (Japan) reported the toxic effect of epirubicin in comparison with doxorubicin. Studies were performed on rats. The authors state that epirubicin is less toxic than doxorubicin. These results are backed up by histologic and morphometric tests.

H. Nakashima et al. (Japan) presented effects of chronic injections of beta-beta-iminodipropionitrile and doxorubicin on chick embryonic cell death. Using the morphometric method, both the number and the size distribution of alpha and gamma motoneurons and spinal ganglion cells were estimated. It was indicated that in embryos treated with beta-beta-iminodipropionitrile both the numbers of alpha and gamma motoneurons were significantly reduced by the 13th embryonic day. In chicks treated with doxorubicin, the number of gamma motoneurons that were selectively reduced was statistically significant and the number of alpha motoneurons was within a normal range.

R.M. Wisner et al. (USA) delivered a very interesting lecture of more general nature. They discussed the realationship between delayed neurotoxic symptoms and a dose of toxic substances placed in fat tissues. In order to explain this issue they used the Hubbard method to reduce toxins in the fat tissue. Transcutaneous current perception thresholds were measured using the Neurometer device in 43 patients before and after treatment with the Hubbard method. The authors conclude that damage of peripheral nerves thought to be permanent may in many cases be partially reversible by the simple expedient of reducing the body burdens of foreign compounds.

Posters were devoted to effects of psychosine in mouse (*A. Komiyama* et al. Japan) . The reason why the study was carried out was an assumption that this toxic metabolite is responsible for demyelination in the PNS of the twitcher mouse (twi/twi), a murine model of globoid cell leukodystrophy in humans. Psychosine is an inhibitor of protein kinase C. The authors conclude that demyelination observed in the twitcher mouse (twi/twi) results from Schwann cell dysfunction.

S. Hayashi et al. (Japan) dealt with the effect of allylnitrile on dopaminergic neurons in rats. It was revealed that allylnitrile enhances the activity of dopaminergic neurons in the nigro-striatal system by interfering with dopaminergic auto-inhibition and/or by inhibiting GABAergic neuron.

M. Miyagawa and *T. Honma* (Japan) focussed on behavioral effects of physostigmine in neostigmine tolerant and non-tolerant rats. The question was whether physostigmine acts peripherally or centrally. The authors drew a conclusion that the assessment of the effect of physostigmine on the central system and peripheral nerves depends upon the type of behaviour used as the index of toxicity.

H. Ito et al. (Japan) investigated effects of polychlorinated biphenyls on regeneration of peripheral nerve in rats. It was revealed that the nerve conduction velocities of the sciatic nerves were slower in the polychlorinated biphenyls group compared with the control group. These results indicated that polychlorinated biphenyls may effect the regeneration of the crushed nerves.

Session 4 devoted to organic solvents and ethylene oxide took place on June 13 and was chaired by Professor *H. Igisu* (Japan). A review lecture was given by *Y. Takeuchi* (Japan).

Polyneuropathy in workers exposed to organic solvents in Japan was the subject of the review lecture. The surveys revealed that hexane, one of the main components in petroleum distillates, is the main agent to cause polyneurpathy. And it also was revealed that hexane has a specific nurotoxicity and its neurotoxicity could be easily modified by other organic solvents like toluene and methylethyl-ketone.

C.W.Cha, E.I. Lee and *D.S. Kim* (Korea) concentrated on peripheral neuropathy in workers exposed to carbon disulphide. Retinopathy, polyneuropathy, brain infart and glomerulosclerosis are considered to be the main late effects of exposure to carbon disulphide. Out of 200 workers who were examined, 150 showed the symptoms of polyneuropathy.

T. Donjo et al. (Japan) investigated olfactory changes following inhalation exposure to 1,1,1 trichloroethane in mice which is commonly used for washing metal accessories. The authors indicated the degeneration of olfactory epithelium, however, after 90 days, that is 85 days since the exposure ceased, the regeneration progressed to complete recovery.

A. Ohnishi, T. Yamamoto and *Y. Murai* (Japan) dealt with the effect of ethylene oxide and propylene oxide on the degeneration of perypheral nerves. They were mostly interested in the degenerative findings in the lumbosacral primary sensory neuron, which easily degenerates when affected by toxic substances. Slow and incomplete regeneration of myelinated axons of the large primary sensory neuron observed in different animal species is important in understanding of pathogenesis of peripheral sensory neuropathies.

H. Nagata et al. (Japan) discussed peripheral neuropathy induced by ethylene oxide in rats. Their studies were connected with a wide use of ethylene oxide in sterilization and disinfection of medical supplies in hospitals and medical disposables. After ^{35}S-methionine injection in the dorsal root ganglion, the velocity of rapid anterograde axonal transport of radioisotope labelled protein was measured and a 33% reduction of the velocity was detected in the neuropathic rats. The authors conclude that a decrease of the velocity of anterograde axonal transport may play a causative role in the development of distal axonal neuropathy due to chronic ethylene oxide exposure.

A poster session or organic solvents included a number of findings namely: *K. Yokoyama* et al. (Japan). Effects of 2,5-hexanedione on glucose utilization rate in the spinal cord of rats; *G. Ichihara* et al. (Japan), Combined effects of hexane and metyhl-ethyl-ketone on the peripheral nerve of the rat; *E. Shibata* et al. (Japan), Cases of peripheral neuropathies associated with the exposure to organic solvents collected in Japan.

In Japan 200 case reports of organic solvent poisoning have been collected since 1983. Out of them there were 37 cases with signs of peripheral neuropathy, 29 cases of occupational poisoning and 8 cases of non-occupational poisoning such as sniffing. The authors are of the opinion that data collected by them are incomplete.

M. Ikeda (Japan) presented subjective symptoms among workers exposed to toluene alone, xylenes alone or a mixture of toluene and xylenes. The author emphesized that subjective symptoms increase together with enhanced concentration of the solvent and that the additiveness assumption is applicable in evaluating the toxicity of a mixture of toluene and xylenes. Surveys were conducted during the years 1985–1989 in China and the groups under study were relatively large (452 persons

of both sexes). The author considered separately symptoms occurring only during exposure at work and those which persisted after work.

T. Eguchi et al. (Japan) analysed vibratory perception threshold and nerve conduction velocity in workers exposed to styrene and toluene. The post-shift urinary concentrations of both mandelic acid and hippuric acid of the workers were used as a measurement of the exposure.

C.C. Huang et al. (Taiwan) presented results of the survey on polyneuropathy after carbon disulphide intoxication obvserved in 1992 in a viscose rayon plant in Taiwan.

K. Miyashita et al. (Japan) found that the upper limit of hearing in workers exposed to styrene and toluene significantly deteriorated.

T. Saito et al. (Japan) presented studies on bond toxic polyneuropathy due do addictive glue sniffing. The authors performed experiments on dogs. The glue contained n-hexane and toluene.

The fifth session focussed on toxic effects of metals. A review paper was presented by *S.S. Chen* et al. (Taiwan). Neurotoxic diseases were observed, among others, after exposure to organic compounds of tin, mercury vapour, lead and others.

The same team of researchers from Taiwan discussed the change of lymphocyte $beta_2$-adrenergic receptors in workers with toxic serum lead levels. It was indicated that in workers lymphocyte $beta_2$-adrenergic receptor density was significantly lower as compared with healthy subjects.

S.D. Kim, S.J. Kim and *C.W. Cha* (Korea) evaluated the effect of inorganic lead on the peripheral nervous system in 12 male workers occupationaly exposed to inorganic lead. A standard electromyogram revealed no abnormalities but in nerve conduction study the abnormal findings were shown. There was no correlation between the abnormal nerve conduction and duration of exposure, blood lead levels and 24 hour urine levels.

K. Takamiya and *M. Kinoshita* (Japan) presneted two cases of neuropathy associated with the use of germanium as an elixir component. The dose of germanium was equal to 35–70 mg of dioxide per day. The autopsy finding showed among others gliosis of the hypoglossal Ncl. and of the oculomotor Ncl. Degeneration and gliosis was also found in the dorsal column of the spinal cord. The renal biopsy showed proximal tubular degeneration and the mitochondrial break down. The concentration of germanium was remarkably high in hair and nails. A several-month clinical observation revealed dysphagia, renal dysfunction and defect of taste sensation.

During the poster session, findings on the methodology were presented, namely: *N. Kamon* (Japan), Quantitaive measurement of thermal threshold using a new thermal perception tester HK-2 and Quantitative measurement of vibratory perception threshold using a new vibrometer TM-31A by the same author. The former device provides a simple and reliable assessment of warm and cold threshold.

The Conference was concluded with a general discussion and a closing address.

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