Scand J Work Environ Health 1983;9(2):214-218

<https://doi.org/10.5271/sjweh.2422>

Issue date: Apr 1983

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/6648421

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Trends and prospects in experimental neurotoxicology

by Heikki Savolainen, MD ¹

SAVOLAINEN H. Trends and prospects in experimental neurotoxicology. *Scand j work environ health* 9 (1983) 214—218. A brief survey is given of the neurotoxic mechanisms of selected industrial compounds. They can be divided for practical purposes into hypoxic or histotoxic mechanisms, reactive metabolite-mediated mechanisms and effects related to the accumulated burden. It is clear that this classification is not necessarily valid for the developing nervous system. Therefore, it is suggested that complete test systems for neurotoxic effects should also include prenatal and neonatal exposure. This inclusion is even more important because a significant proportion of embryotoxic or teratogenic effects are related to deleterious changes in the nervous system. An understanding of these developmental effects should also help in the design of epidemiologic studies.

Key words: fetal and developmental toxicity, industrial neurotoxins, neurotoxicity test systems.

Poisoning episodes have brought about the importance of neurotoxicology as an independent discipline which would have lessened the deleterious effects of thalidomide in Central Europe (37), of methylmercury in Iraq (2), Canada (62) or Japan (12), of allylchloride in China (20), or of clioquinoline in Japan (59) and Europe (3).

Experimental neurotoxicology has aided in the elucidation of the mechanism of pathogenesis in the occupational neuropathies in exposure to carbon disulfide or hexacarbon ketones or hexane [for a review see an earlier report (53)]. The understanding of toxic mechanisms allows unifying theories and consequently classifications of neurotoxic compounds superior to those based on the direct comparison of effects and the offending agent

(10, 45), which renders the lists long and perhaps impossible to memorize.

Many neurotoxins have gone undetected so far (19) because no single experimental detection technique is sensitive or specific enough if applied alone (42). This circumstance is due to the fact that the nervous system functions cannot be defined as readily as, eg, that of the liver or kidneys. Behavior is an important product of the brain, and yet the nervous system also controls and maintains many other organ systems by endocrinologic means, by direct innervation and electric stimulation, or through the so-called trophic control by modulatory protein molecules delivered directly and specifically to the appropriate cells. The nervous system also actively participates in the control of development and maturation in the fetal and early postnatal period.

It is the aim of this treatise to present some of the key issues and try to outline future trends for test systems based on the newer advances in the neurosciences. These methods are hopefully more powerful in the detection of toxic effects.

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Aspects of neurotoxic mechanisms in the adult nervous system

The nervous system is vulnerable to the deprivation of oxygen and to the histotoxic or hypoxemic effects of hydrogen sulfide (53), hydrogen cyanide (64), carbon monoxide (65), and formic acid (55, 66, 67).

The acutely intoxicating effects of inhaled solvent vapors are known to those engaged in producing paints, glues and lacquers or applying solvent-based coatings or operating degreasing installations. It seems that the inhaled lipophilic molecules are rapidly carried to the nervous system across the blood-brain barrier and that they are incorporated in the excitable membranes where they cause an increased fluidity of the semi-fluid system which impairs the ionic conductance and formation of action potentials (47). Chronically or repeatedly exposed subjects acquire a tolerance towards these fluidizing effects so that isomolar doses no longer cause equivalent effects [for a review see an earlier report (53)]. This tolerance is nonspecific so that, eg, cells adapted to ethanol show similar adaptation towards other alcohols (34).

It is not often that these acutely intoxicating effects are of appreciable concern in the industrial setting. However, chronic neurotoxicity of, eg, n-hexane and its metabolites is a recognized hazard in trades extending from the shoe industry to coated fabrics plants (1, 4). The chronically toxic effects may depend on the formation of more toxic metabolites in the nervous system (52). Nervous system cells contain a capacity for required metabolic activation (36, 43) although it is not certain whether the activity can be induced (22) as is the rule in the liver.

Water-soluble contaminants, like many metal ions, do not penetrate the blood-brain barrier as the lipid-soluble compounds do. This situation implies that a threshold concentration must be overcome before nervous system toxicity may be seen. Protection is therefore afforded for the neurons from, eg, the direct toxicity of mercury or lead, while there is also the drawback that ions accumulated at the protective barriers are not subject to similar rapid removal as material in the blood. Thus lead accumulates in the brain

(29) and in the sciatic nerve (21) during continued exposure even if the transmitting blood compartment is in a virtual steady state. According to this hypothesis, the accumulated osmotically active lead increases the fluid pressure in the peripheral nerves and causes the neuropathy (63). Analogous mechanisms could account for diabetic (13) and galactosemic (40) neuropathies. For practical purposes, the neurotoxic effects in adults can be divided into three categories that can be summarized as follows: (i) agents causing hypoxic and histotoxic hypoxia (carbon monoxide, hydrogen sulfide, hydrogen cyanide, organic nitriles, formic acid, many products of polymeric thermal degradation), (ii) agents with reactive intermediates (trichloroethylene, carbon disulfide, n-hexane, styrene, vinyltoluene, methyl cellosolve), and (iii) agents with accumulation and burden-related effects (cadmium, lead, mercury, chlorinated and brominated biphenyls, dibenzodioxins, furans).

Fetal and developmental neurotoxicity

There is no doubt about the delivery of many maternal xenobiotics in the developing fetus (11, 18, 38) although it is equally convincing that a number of effects are maternally mediated (27, 39). Therefore, it is futile to describe only the teratogenic effects of any chemical without trying to analyze its concentration in the developing offspring.

The maturation of the human central nervous system extends several years into the postnatal period in morphological (25) as well as biochemical terms (54). Significant intrauterine events are the formation and closure of the neural tube on gestation days 22 to 26, while the first major migration of cerebral neuroblasts to their eventual locations occurs at days 43 to 90. Consequently the neocortex is formed within the period of the third to the eighth gestational month. For comparison the encephalic vascularization is more or less complete within the third gestational month.

As true mutations are rare causes of major structural anomalies or behavioral deficits (16, 23, 44), exposure to a poten-

tially toxic chemical must occur within the appropriate critical period (46) to cause the specific outcome. Thus encephaloclastic lesions with arrested neuroblastic migration can only be caused in early pregnancy (41), while the cause of holoprosencephaly and agenesis of the corpus callosum may be traced to a later period (26).

On the whole, the migration of cells and the constitution of cellular contacts are subject to complicated biochemical and morphological surface modifications (14) and to subsequent interactions of neuronal and glial cells (8) so that the final locations are achieved (5). It is currently believed that the axon elongation that follows later is guided by cells of nonneuronal origin already at their locations (15).

Reciprocally the outgrowing axon controls, eg, the development of a limb by secreting a trophic agent (35). Amelia, or malformed limb, was the result of exposure in utero to thalidomide (37), and there is a strong case that the primary cause was the degeneration of the relevant axons [for a review see an earlier report (37)]. However, outgrowing axons do not control all developing structures (61), and also motor nerve branches fail to form in chick wings devoid of muscle (30).

Apart from failure to form the proper anatomical faculties, chemicals can also inhibit biochemical maturation. A single injection of methylazoxymethanol to pregnant rats on the 15th day of gestation causes arrest of myelination in the offsprings with resultant behavioral deficits (60). L-cysteine dosed to neonatal rats causes specific behavioral deficits in later life by the destruction of already formed neurons in the hippocampus (57). Likewise, reserpine given to 11-day-old rats in a single dose hinders DNA (deoxyribonucleic acid) synthesis in the forebrain (31), and a single injection of methylmercury to pregnant golden hamsters produces degenerative changes in fetal neuroblasts (48), which remain in the adult animals and even cause progressive damage (49).

There are indications that most xenobiotics enter the developing brain more readily than they do in adults. The blood-brain barrier matures in the postnatal period (7, 9). This fact is reflected by the

finding that encephalopathy is the presenting sign of lead toxicity in children (33), while neuropathic changes are found in adults (56).

Comments

The testing of chemicals for neurotoxicity should include experiments in the fetal and neonatal period as is urged for protocols to reveal carcinogens (17). However, counts of malformed fetuses do not suffice. The developing nervous system elements are amenable to isolation and biochemical analysis (50, 51), and the specimens can also be subjected to morphological analysis. This procedure would greatly expand the predictive scope of the tests.

For newborn babies, birthweight is a good clinical predictor for neurobehavioral performance (28, 32). Learning-disabled children also have abnormal head circumference, above or below the mean of controls ± 3 SD (6, 58). A sound epidemiologic study on the teratogenic effects of a chemical should therefore include birthweight data and, preferably also, head circumference. A good correlation, eg, with a mother's smoking habit (18) and ethanol abuse (24) exists.

The intention is clearly not to expand the existing testing schemes but to modify them according to recent advances in toxicology. The rigid testing guidelines should be abandoned and replaced by tiered systems according to specific needs.

References

1. Aiello I, Rosati G, Serra G, Manca C. Subclinical neuropathic disorders and precautionary measures in the shoe industry. *Acta neurol* 35 (1980) 285–292.
2. Amin-Zaki L, Majeed MA, Elhassani SB, Clarkson TW, Greenwood MR, Doherty RA. Prenatal methylmercury poisoning: Clinical observations over five years. *Am j dis child* 133 (1979) 172–177.
3. Baumgartner G, Gawel MJ, Kaeser HE, Pallis CA, Clifford FR, Schaumburg HH, Thomas PK, Wadia NH. Neurotoxicity of halogenated hydroxyquinolines: Clinical analysis of cases reported outside Japan. *J neurol neurosurg psychiatry* 42 (1979) 1073–1083.
4. Billmaier D, Yee HT, Allen N, Craft B, Williams N, Epstein S, Fontaine R. Periph-

- eral neuropathy in a coated fabrics plant. *J occup med* 16 (1974) 665—671.
5. Blechschmidt E. The programming of afferent and efferent nervous fibers in man. *Arch Psychiatr Nervenkr* 224 (1977) 259—272.
6. Brandt I. Kopfumfang und Gehirnentwicklung. Wachstumsretardation bei intrauteriner Mangelversorgung und ihre Aufholmechanismen. *Klin Wochenschr* 59 (1981) 995—1007.
7. Braun LD, Cornford EM, Oldendorf WH. Newborn rabbit blood-brain barrier is selectively permeable and differs substantially from the adult. *J neurochem* 34 (1980) 147—152.
8. Choi BH, Lapham LW. Interactions of neurons and astrocytes during growth and development of human fetal brain *in vitro*. *Exp mol pathol* 24 (1976) 110—125.
9. Cremer JE, Braun LD, Oldendorf WH. Changes during development in transport processes of the blood-brain barrier. *Biochim biophys acta* 448 (1976) 633—637.
10. Damstra T. Environmental chemicals and nervous system dysfunction. *Yale j biol med* 51 (1978) 457—468.
11. Dencker L. Embryonic-fetal localization of drugs and nutrients. In: Persaud TVN, ed. *Teratogenic mechanisms*. MTP Press, New York, NY 1979, pp 1—18.
12. Eto K, Takeuchi T. Pathological changes of human sural nerves in Minamata disease (methylmercury poisoning): Light and electron microscopic studies. *Virchows arch B cell pathol* 23 (1977) 109—128.
13. Fagius J, Jameson S. Effects of aldose reductase inhibitor treatment in diabetic polyneuropathy — A clinical and neurophysiological study. *J neurol neurosurg psychiatry* 44 (1981) 991—1001.
14. Freeman BG. Surface modifications of neural epithelial cells during formation of the neural tube in the rat embryo. *J embryol exp morphol* 28 (1972) 437—448.
15. Gottlieb DI. The blueprint hypothesis of axon guidance. *Nature* 283 (1980) 428.
16. Grace HJ, Ally FE, Nelemans AP, Kint B. A cytogenetic study of a mentally retarded population in South Africa. *S afr med j* 55 (1979) 707—709.
17. Grice HC, Munro IC, Krewski DR. *In utero* exposure in chronic toxicity/carcinogenicity studies. *Food cosmet toxicol* 19 (1981) 373—379.
18. Harrison KL, Robinson AG. The effect of maternal smoking on carboxyhemoglobin levels and acid-base balance of the fetus. *Clin toxicol* 18 (1981) 165—168.
19. Hay A. Neurotoxins may go unrecognised. *Nature* 274 (1978) 206.
20. He F, Shen D, Guo Y, Lu B. Toxic polyneuropathy due to chronic allyl chloride intoxication: A clinical and experimental study. *Chin med j* 93 (1980) 177—182.
21. Hietanen E, Kilpiö J, Närhi M, Savolainen H, Vainio H. Biotransformational and neurophysiological changes in rabbits exposed to lead. *Arch environ contam toxicol* 9 (1980) 337—348.
22. Hook GER, Haseman, JK, Lucier GW. Induction and suppression of hepatic and extrahepatic microsomal foreign compound metabolizing enzyme systems by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Chem biol interact* 10 (1975) 199—214.
23. Iivanainen M. A study on the origins of mental retardation. Spastics International Medical Publications, London 1974, pp 1—73. (Clinics in developmental medicine, no 51).
24. Iosub S, Fuchs M, Bingol N, Gromisch DS. Fetal alcohol syndrome revisited. *Periatrics* 68 (1981) 475—479.
25. Jacob H. Neurobiologie der Lebensalter. *Fortschr Neurol Psychiatr ihrer Grenzgeb* 44 (1976) 617—633.
26. Jellinger K, Gross H, Kaltenböck E, Grisold W. Holoprosencephaly and agenesis of the corpus callosum: Frequency of associated malformations. *Acta neuropathol* 55 (1981) 1—10.
27. Klein NW, Plenefisch JD, Carey SW, Fredrickson WT, Sackett GP, Burbacher TM, Parker RM. Serum from monkeys with histories of fetal wastage causes abnormalities in cultured rat embryos. *Science* 215 (1982) 66—69.
28. Kurtzberg D, Vaughan HG Jr, Daum C, Grellong BA, Albin S, Rotkin L. Neurobehavioral performance of low-birthweight infants at 40 weeks conceptional age: Comparison with normal fullterm infants. *Dev med child neurol* 21 (1979) 590—607.
29. Larmo M, Savolainen H. Nervous system porphyrins in low-level peroral lead exposure. *Exp neurol* 74 (1981) 260—264.
30. Lewis J, Chevallier A, Kieny M, Wolpert L. Muscle nerve branches do not develop in chick wings devoid of muscle. *J embryol exp morphol* 64 (1981) 211—232.
31. Lewis PD, Patel AJ, Béndek G, Balász R. Do drugs on the nervous system affect cell proliferation in the developing brain? *Lancet* 1 (1977) 399—401.
32. Lipper E, Lee K, Gartner LM, Grellong B. Determinants of neurobehavioral outcome in low-birth-weight infants. *Pediatrics* 67 (1981) 502—505.
33. Lin-Fu JS. Lead exposure among children — A reassessment. *New engl j med* 300 (1979) 731—732.
34. Lyon RC, McComb JA, Scheurs J, Goldstein DB. A relationship between alcohol intoxication and the disordering of brain membranes by a series of short-chained alcohols. *J pharmacol exp ther* 218 (1981) 669—675.
35. Maden M. Neurotrophic and X-ray blocks in the blastemal cell cycle. *J embryol exp morphol* 50 (1979) 169—173.
36. Marietta MP, Vesell ES, Hartman RD, Weisz J, Dvorchik BH. Characterization of cytochrome P-450-dependent aminopyrine N-demethylase in rat brain: Comparison with hepatic aminopyrine N-demethylation. *J pharmacol exp ther* 208 (1979) 271—279.
37. Mc Bride WG. The pathogenesis of thalidomide embryopathy. In: Persaud TVN, ed.

- Teratogenic mechanisms. MTP press, New York, NY 1979, pp 113—127.
38. McClain RM, Becker BA. Teratogenicity, fetal toxicity, and placental transfer of lead nitrate in rats. *Toxicol appl pharmacol* 31 (1975) 72—82.
 39. Millicovsky G, DeSesso JM, Kleinman LI, Clark KE. Effects of hydroxyurea on hemodynamics of pregnant rabbits: A maternally mediated mechanism of embryotoxicity. *Am j obstet gynecol* 140 (1981) 747—752.
 40. Myers RR, Costello ML, Powell HC. Increased endoneurial fluid pressure in galactose neuropathy. *Muscle nerve* 2 (1979) 299—303.
 41. Norman MG. Bilateral encephaloclastic lesions in a 26 week gestation fetus: Effect on neuroblast migration. *Can j neurol sci* 7 (1980) 191—194.
 42. Norton S. Is behavior or morphology a more sensitive indicator of central nervous system toxicity? *Environ health perspect* 26 (1978) 21—27.
 43. Oftebro H, Størmer FC, Pedersen JJ. The presence of an adrenodoxin-like ferredoxin and cytochrome P-450 in brain mitochondria. *J biol chem* 254 (1979) 4331—4334.
 44. Opitz JM. Diagnostic/genetic studies in mental retardation. *Postgr med* 66 (1979) 205—214.
 45. Prockop L. Neurotoxic volatile substances. *Neurology* 29 (1979) 862—865.
 46. Rodier PM. Critical periods for behavioral anomalies in mice. *Environ health perspect* 18 (1976) 79—83.
 47. Roth SH. Physical mechanisms of anesthesia. *Annu rev pharmacol toxicol* 19 (1979) 159—178.
 48. Reuhl KR, Chang LW, Townsend JW. Pathological effects of *in utero* methylmercury exposure on the cerebellum of the golden hamster: I Early effects upon the neonatal cerebellar cortex. *Environ res* 26 (1981) 281—306.
 49. Reuhl KR, Chang LW, Townsend JW. Pathological effects *in utero* methylmercury exposure on the cerebellum of the golden hamster: II Residual effects on the adult cerebellum. *Environ res* 26 (1981) 307—327.
 50. Savolainen H. Proteins of human cortical neurons during development. *Neurobiology* 2 (1972) 89—95.
 51. Savolainen H. Differentiation of human cortical neurons: Proteins of subcellular particles. *Comp biochem physiol B* 44 (1973) 467—472.
 52. Savolainen H. Some aspects of the mechanisms by which industrial solvents produce neurotoxic effects. *Chem biol interact* 18 (1977) 1—10.
 53. Savolainen H. Neurotoxicity of industrial chemicals and contaminants: Aspects of biochemical mechanisms and effects. *Arch toxicol* (1982): suppl 5, 71—83.
 54. Savolainen H, Palo J, Riekkinen P, Mörönen P, Brody LE. Maturation of myelin proteins in human brain. *Brain res* 37 (1972) 253—263.
 55. Savolainen H, Zitting A. Glial cell effects of subacute formic acid vapour exposure. *Acta pharmacol toxicol* 47 (1980) 239—240.
 56. Seppäläinen A-M, Hernberg S, Kock B. Relationship between blood lead levels and nerve conduction velocities. *Neurotoxicology* 1 (1979) 313—332.
 57. Sharpe LG, Olney JW, Ohlendorf C, Lyss A, Zimmerman M, Gale B. Brain damage and associated behavioral deficits following the administration of L-cysteine to infant rats. *Pharmacol biochem behav* 3 (1975) 291—298.
 58. Smith RD. Abnormal head circumference in learning-disabled children. *Dev med child neurol* 23 (1981) 626—632.
 59. Tsuji S, Fujishima H. Paraplegias, clinical statistics. Kyushu Rosai Hospital, Department of Orthopedics and Neurology, Fukuoka 1975.
 60. Tsukada Y, Nomura M, Nagai K, Kohsaka S, Kawahata H, Ito M. Neurochemical correlates of learning ability. In: Delgado JMR, De Feudis FV, ed. *Behavioral neurochemistry*. Spectrum Publications, New York, NY 1977, pp 63—85.
 61. Wertz RL, Donaldson DJ. Effects of x-rays on nerve-dependent (limb) and nerve-independent (jaw) regeneration in the adult newt. *J embryol exp morphol* 53 (1979) 315—325.
 62. Wheatley B, Barbeau A, Clarkson TW, Lapham LW. Methylmercury poisoning in Canadian Indians — The elusive diagnosis. *Can j neurol sci* 6 (1979) 417—422.
 63. Windebank AJ, Dyck PJ. Kinetics of ^{210}Pb entry into the endoneurium. *Brain res* 225 (1981) 67—73.
 64. Vogel SN, Sultan TR, Ten Eyck RP. Cyanide poisoning. *Clin toxicol* 18 (1981) 367—383.
 65. Zimmerman SS, Truxal B. Carbon monoxide poisoning. *Pediatrics* 68 (1981) 215—224.
 66. Zitting A, Savolainen H. Biochemical effects of subacute formic acid vapor exposure. *Res commun chem pathol pharmacol* 27 (1980) 157—162.
 67. Zitting A, Savolainen H, Nickels J. Biochemical and toxicological effects of single and repeated exposures to polyacetal thermodegradation products. *Environ res* 29 (1982) 287—296.