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Organophosphate-Induced Delayed Neuropathy

Marion Ehrich and Bernard S. Jortner

1. INTRODUCTION/HISTORY

Although the cholinesterase-inhibiting effects of organophosphate (OP) compounds were not utilized until the time of World War II, the ability of some of these chemicals to cause an irreversible, progressive delayed neuropathy was recognized as early as the 1890s, when a 15% solution of tri-*ortho*-cresyl phosphate (TOCP, or tri-*ortho*-tolyl phosphate, TOTP) was used to treat tuberculosis. A number of incidents of organophosphate-induced delayed neuropathy (OPIDN) have been reported since then, with TOTP identified as the neurotoxic contaminant of cresyl phosphates associated with these poisonings. Large numbers of humans were affected in some of these incidents, including over 50,000 Americans who ingested a TOTP-contaminated alcoholic extract of ginger during the era of prohibition (1930s), 10,000 Moroccans who ingested TOTP-contaminated cooking oil in the 1950s, and 600 Indians who consumed TOTP-contaminated rapeseed oil in 1988. Early studies determined that not every OP compound was capable of causing OPIDN and that all animal species were not uniformly susceptible. Clinical evidence of progressive, irreversible OPIDN has been observed in humans, water buffalo, sheep, cats, ferrets, chickens, and a number of other species; laboratory rodents (e.g., rats, mice), however, do not demonstrate progressive locomotor effects after exposure *(1–7).*

TOTP has been associated with the largest number of cases of OPIDN observed in people, but OP compounds initially but no longer manufactured as pesticides (e.g., leptophos, mipafox, O-ethyl-O-*p*-nitrophenyl phenylphosphonothioate [EPN]) were also responsible for a number of accidental poisonings of humans and animals. To reduce risk for OPIDN in humans and susceptible animals of economic importance, US Environmental Protection Agency (EPA)-required testing procedures are now used and OP compounds capable of inducing OPIDN in the absence of significant (i.e., lethal) cholinesterase inhibition are not currently marketed for use as insecticides in the United States *(8).* Some compounds that cause OPIDN elict this syndrome at dosages that also cause acute toxicity as a result of cholinesterase inhibition (e.g., EPN, diisopropyl phosphorofluoridate [DFP]). A number of other delayed neuropathy-inducing OP com-

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Table 1
Examples of Neuropathy-Inducing OP Compounds

Name or abbreviation	*Chemical name*	*Current or former use*
TOCP	Tri-*ortho*-cresyl phosphate	Lubricant, fuel additive, manufacture of plastics
TOTP	Tri-*ortho*-tolyl phosphate	
DFP	Diisopropyl phosphorofluoridate; difluorophosphate	Nerve gas
Mipafox	*N,N'*-diisopropyl phosphorodiamidofluoridate	Insecticide
Leptophos	*O*-4-bromo-2,5-dichlorophenyl *O*-methyl phenyl phosphorothioate	Insecticide
EPN	*O*-ethyl O-*p*-nitrophenyl phenylphosphonothioate	Insecticide
Methamidophos	O,S-dimethyl phosphorothioamidate	Insecticide

pounds are not notable inhibitors of cholinesterase (e.g., TOTP), and are used as lubricants, fuel additives, and in the manufacture of plastics. Today such products are formulated to decrease the neuropathy-inducing component *(4,9)*. Tables of neuropathy-inducing OP compounds and their chemical structures are included in several previous reviews *(1,2,5,10)*. An abbreviated list is provided in Table 1. Although no specific structural features that positively identify a neuropathy-inducing OP compound have been identified, structure activity studies have noted that the phosphorus must be in a pentavalent state, the atom attached with the coordinate covalent bond to the phosphorus must be an oxygen, at least one oxygen must bridge an R group to the phosphorus, and increased hydrophobicity can increase neuropathy-inducing capability among a series of neuropathy-inducing OP analogs (11).

Another type of delayed neuropathy that may follow administration of OP compounds (termed type II delayed neurotoxicity) has been described. Compounds inducing this syndrome have a trivalent phosphorus atom. Differences between type II delayed neurotoxicity and classical OPIDN can be noted in time to onset and manifestations of clinical signs and in location and spectrum of neuropathological lesions. Further information on type II delayed neurotoxicity induced by trivalent OP compounds can be found in other reviews *(2,11,12)*.

2. CLINICAL AND MORPHOLOGICAL EVIDENCE OF OPIDN IN MAN AND ANIMALS

OPIDN can occur in humans and in a number of animal species following single or multiple exposures. The symptoms, which do not appear for days to weeks after exposure, are progressive and irreversible, although some improvement has been reported over time *(2,13)*. Clinical features of OPIDN in man have been described. OPIDN begins with sensory loss in hands and feet, but exclusively sensory neuropathy is not a

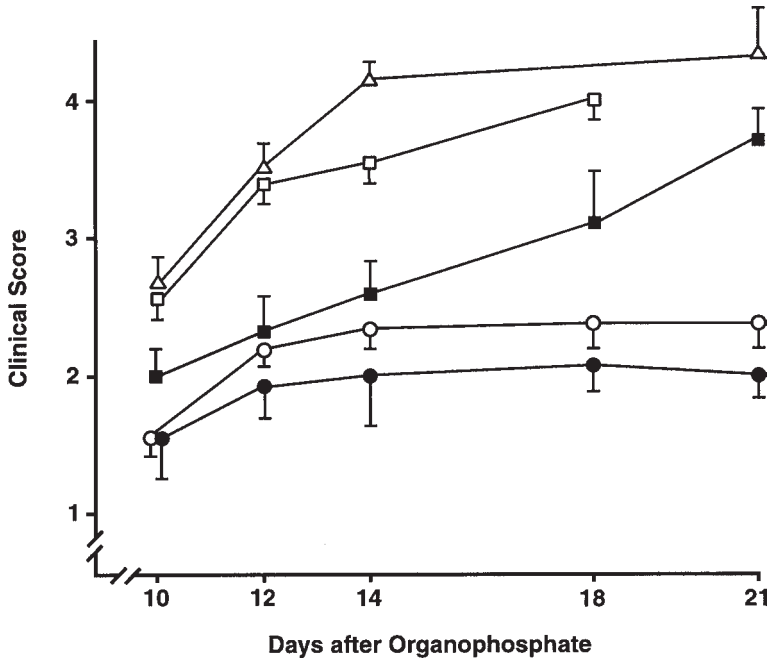


Fig. 1. Development of clinical signs in chickens after administration of phenyl saligenin phosphate (PSP) and tri-*ortho*-tolyl phosphate (TOTP). Results are presented as mean ± SD, $n = 3$ –9. PSP im 2 mg/kg (❍ – ❍), 3 mg/kg (□ – □), 10 mg/kg (Δ – Δ); TOTP 360 mg/kg po (• – •), 500 mg/kg po (■ – ■). Increasing clinical scores reflect progression of deficits. Reprinted with permission from ref. *15*, ©Intox Press.

feature in humans. Motor alterations such as slowed conduction and, eventually, bilateral and symmetrical weakness progressing to flaccidity of the distal skeletal muscles of the lower and upper extremities occur. The patient notices tingling then loss of feeling in hands and feet, locomotor difficulties, and abnormal reflexes *(4,10,11,14).*

In animals as well as man, there is a latent period between exposure and manifestations of OPIDN. The domestic chicken (hen) is the recognized animal model for OPIDN *(8).* Effects on the legs are noted, and the hen exhibits progressive incoordination and difficulty in walking *(*Fig. 1; *15*). Eventually ability to walk is lost and the wings, too, become involved. There is an age-related susceptibility, in that these effects are not seen in chickens less than 55 d of age. Progressive ataxia is also seen in adults of other susceptible species (e.g., cats, sheep, water buffalo, horses, ferrets). Ataxia has not been a prominent feature of OPIDN in rodents *(1,3,11,16–18).*

The neuropathologic changes in classical (type I) OPIDN are typified by those elicited in experimental animals such as the chicken, cat and ferret dosed with compounds such as TOTP, DFP, or phenyl saligenin phosphate (PSP). These relate well to the observed clinical deficits and consist of degeneration of distal regions of large, long myelinated axons as the primary lesion, which progresses to Wallerian-like degeneration of affected fiber regions *(19).* The primary lesion is thought to reside in a distal nonterminal axonal region, with subsequent somartofugal extension of the alterations to the terminal axons and their endings *(20–23).* Lesions generally become apparent at

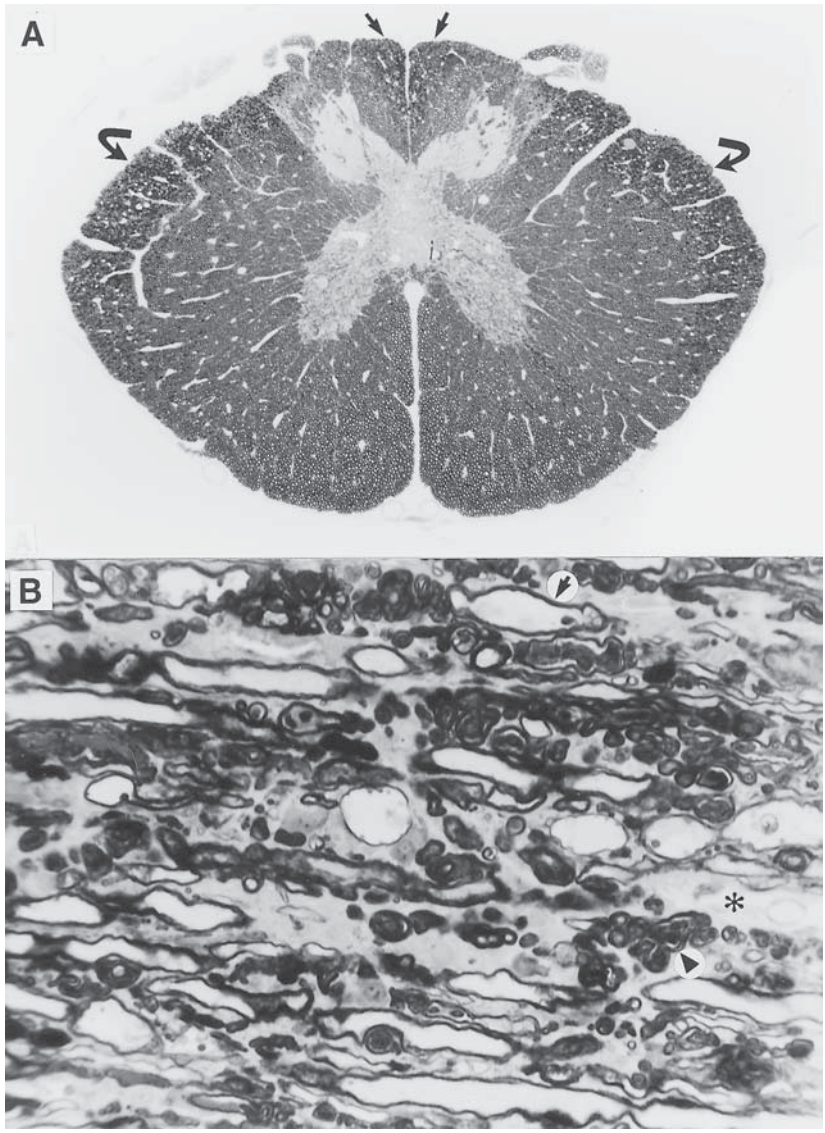


Fig. 2. Organophosphorus-induced delayed neuropathy. **(A)** Low-power view of darkly stained bilateral degeneration of fasciculus gracilis (straight arrows) and spinocerebellar tracts (curved arrows) in a transversely stained cervical spinal cord. **(B)** Higher-power longitudinal section showing swollen axons with attenuated myelin sheaths (arrow), dark staining masses of myelin-rich debris (arrowhead) and replacement of degenerated fibers by pale-stained regions of astrocytic proliferation.* Both sections from a hen dosed with 1 mg/kg DFP 21 d earlier, toluidine blue and safranin stain.

or close to the end of the symptom-free postdosing period, and increase in severity and proximal extent associated with progressing clinical deficits. Regions of pathologic involvement include bilateral distal regions of long peripheral nerves and of brain or spinal cord long tracts such as fasciculus gracilis, and spinocerebellar, spinolivary, rubrospinal reticulospinal, and medial pontine spinal (hens only) tracts (Fig. 2) *(19,23–30).* Neuronal-cell bodies are spared *(19,24).*

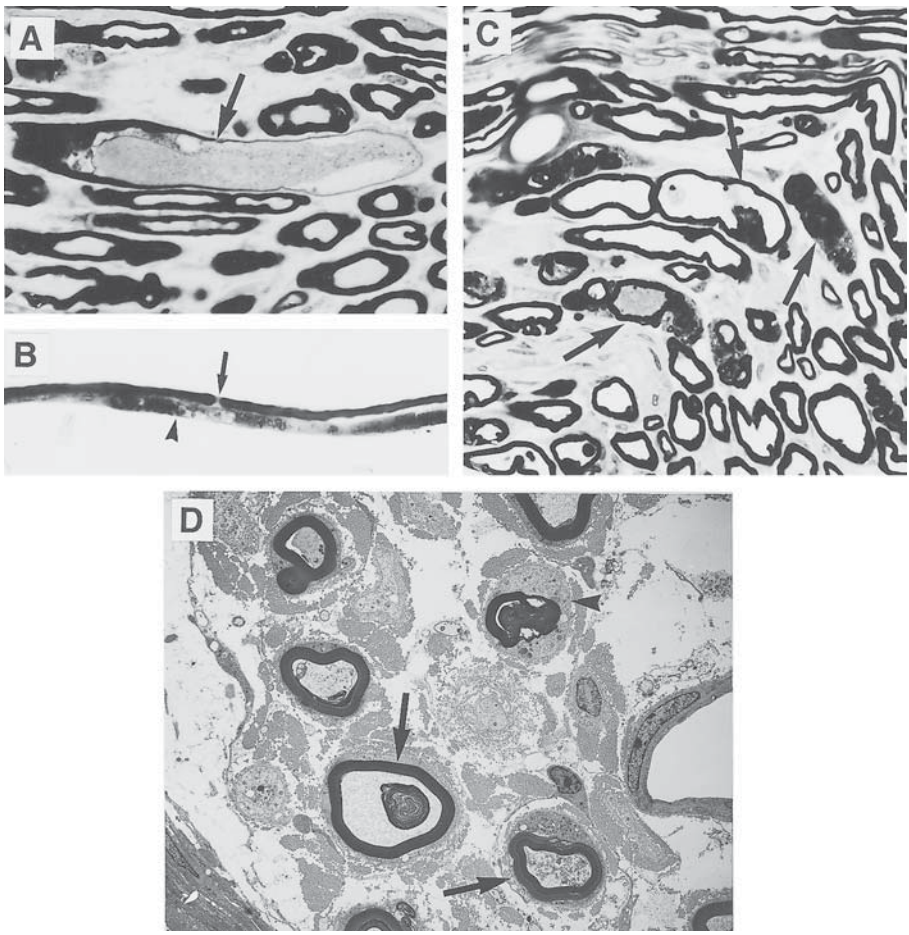


Fig. 3. Photographs are of tibial nerve branch to gastrocnemius muscle of hens dosed with a single neurotoxic doses of phenyl saligenin phosphate **(A–C)** or the dorsal metatarsal nerve of hen dosed with diisopropyl phosphofluoridate **(D)**. **(A)** Tangential section of swollen degenerating axon with thin (attenuated) myelin sheath (arrow). Day 9. Toluidine blue and safranin stain (also used in C). **(B)** Intact myelinated fiber (arrow points to node of Ranvier) and an adjacent fiber in Wallerian-like degeneration (arrowhead). Day 14, teased fiber preparation, osmium tetroxide stain. **(C)** Tangential section showing various stages of myelinated fiber degeneration (arrows). Day 15. **(D)** Cross-section showing axonopathic changes (arrows) to advanced Wallerian-like degeneration (arrowhead). Increased endoneural space suggests edema. Reproduced from *Toxicologic Pathology* with the permission of The Society of Toxicologic Pathologists *(31).*

The morphologic features of the nerve fiber lesions include swelling of affected axons (generally the long, large fibers) leading to attenuation of their myelin sheaths (Figs. 2 and 3; *31*). The affected axons may demonstrate proliferation of tubules and cisterns, vacuoles (also affecting inner myelin sheaths), disorganized masses of abnormal mitochondria, cytoskeletal elements, dense bodies, and membranous multilamellar bodies *(20–23,32).* This appears to progress to granular degeneration of axonal contents, yielding swollen, electron-lucent axoplasm (Fig. 3). Another axonal alteration,

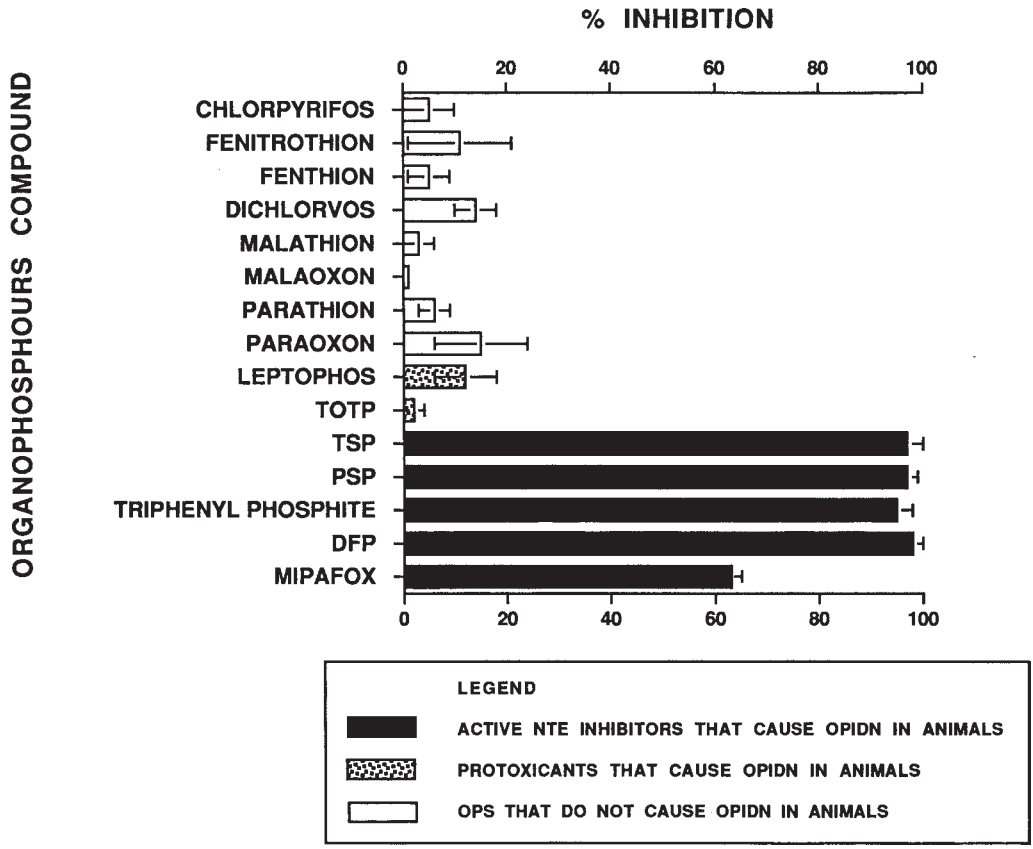


Fig. 4. NTE inhibition in SH-SY5Y cells exposed to OP compounds. Human neuroblastoma cells (1×10^7 cells/mL in saline) were exposed for 1 h to concentrations of 10^{-5} *M*. DFP, mipafox, TSP, triphenyl phosphite, and PSP are active NTE inhibitors and agents that induce OPIDN in animal models. TOTP and leptophos are protoxicants that require metabolic activation before NTE can be inhibited. The protoxicant parathion and its active oxon congener, paraoxon, as well as malathion and malaoxon, do not induce OPIDN in the hen model. Additional protoxicants are chlorpyrifos, fenthion, and fenitrothion. Dichlorvos is an active inhibitor of acetylcholinesterase, but is not likely to induce OPIDN in the hen model. Results are expressed as mean ± SEM of results from 3–7 different days on which assays were done. Reprinted with permission from ref. *35*; ©Taylor & Francis.

common in affected myelinated tracts of the central nervous system (CNS), is atrophic, dark-staining axons containing only diminished, electron-dense, amorphous axoplasm *(15)*. This change is associated with disaggregating myelin sheaths. Degradation of axonal contents is thought to be associated with enhanced axonal activity of calcium-activated proteases *(33)*. As noted earlier, these lesions progress to Wallerian-like fragmentation of affected fiber regions, with phagocytosis and myelin ovoid formation (Fig. 3). The latter are prominent in peripheral nerve. In peripheral nerve there is also subsequent breakdown of phagocytized fiber debris and proliferation of columns of Schwann cells within their basal lamina sheaths. This provides an environment allowing significant myelinated fiber regeneration following OPIDN *(13,34)*. The myelinated fiber degen-

eration in the central nervous system evolves more slowly, and is associated with proliferation of astrocytes (astrocytosis) in affected tracts *(13)* (Fig. 2). As might be expected, regeneration of spinal-cord or brain fibers is not a feature of OPIDN *(13)*. Studies using the Fink-Heimer silver impregnation method revealed a greater spectrum of OPIDN spinal cord and brain lesions. These consisted of degenerating small axons and synaptic boutons in spinal gray matter and some medullary and cerebellar nuclei *(29,30)*.

3. MECHANISMS OF ACTION/TREATMENTS

The initial event that occurs in the nervous system within hours after exposure to neuropathy-inducing OP compounds is inhibition of a carboxylesterase called neuropathy target esterase (NTE, also known as neurotoxic esterase). OP compounds that do not induce OPIDN do not inhibit this enzyme (Fig. 4; *35*). Inhibition of this enzyme requires the oxon form of the OP compound; P = S compounds and TOTP are protoxicants that require metabolism before NTE is inhibited and OPIDN can be induced. Not only must OP compounds inhibit NTE, but the inhibition must be significant (e.g., about 70% or more after acute administration; approx 50% after multiple exposures) and the interaction between the OP compound and NTE must be so strong that the inhibition essentially irreversible. Without these features, neuropathy will not develop. For most OP compounds that essentially irreversibly inhibit NTE, a leaving group causes the OP compound–NTE complex to become charged, a process known as "aging." Pretreatment of experimental animals with reversible inhibitors of NTE prevents OP-induced inhibition and aging and protects exposed subjects from OPIDN *(5,36)*.

Although inhibition of NTE is a necessary antecedent to OPIDN, the precise relationship between NTE and OPIDN has not been defined. The physiological function of NTE is unknown, so the significance of OP-induced inhibition is unknown. NTE is present in brain, spinal-cord, and peripheral nerves, as well as in non-neural cells (e.g., lymphocytes), but no adverse effects of OP-induced inhibition have been noted outside the nervous system. Inhibition is notable in brain, but this tissue is not a major site of injury in OPIDN. Furthermore, NTE can be inhibited just as significantly in animals not demonstrating clinical evidence of this disorder (e.g., chicks, rodents) as it is in susceptible species. Continued NTE inhibition is not necessary for OPIDN, as activity may be back to pre-exposure levels before clinical signs appear and morphological evidence of the neuropathy develops. The relationship between NTE inhibition and OPIDN has been further complicated in recent years by the discovery that administration of a reversible NTE inhibitor after administration of a neuropathy-inducing OP compound results in exacerbation (promotion) of the OPIDN beyond that which would have been expected by the OP compound alone. This promotion can occur even when NTE is maximally inhibited by the first compound given, suggesting the possibility of an additional, nonesterase site of action for OPIDN promotion *(11,37–41)*.

NTE has been a difficult enzyme to purify. It is a serine esterase that is an integral membrane protein with a molecular weight of approx 155 kDa, although a soluble isoform present only in peripheral nerve has recently been described and characterized *(42)*. Immunostaining of the recently purified enzyme indicated that was present in essentially all neurons and that immunostaining was not altered by treatment with neuropa-

thy-inducing OP compounds. Its structure has reasonable similarity with that of an insect neuronal protein that interrupts the relationship between neurons and glial cells, leading to apoptosis of both. It has been, therefore, suggested that NTE plays a role in cell signaling during development *(43)*.

The precise temporal sequence of events that occur between NTE inhibition and onset of clinical and pathological manifestations of OPIDN is as yet unclear. Alterations in threshold excitability of peripheral nerves, axonal transport, neurotrophic factors, protease activity, and protein phosphorylation have all been reported in the interval between NTE inhibition and the onset of OPIDN *(2,11,36,37,44)*.

In addition to the modifications of OPIDN in the presence of reversible NTE inhibitors noted earlier, clinical, electrophysiological, and morphological endpoints indicative of OPIDN can be ameliorated by pretreatment with corticosteroids or calcium-channel blockers. These treatments did not, however, affect OP-induced NTE inhibition. They could, however, be affecting events that occur subsequent to NTE inhibition and prior to manifestations of OPIDN *(37)*.

4. FUTURE DIRECTIONS

Studies on OPIDN are likely to continue even though few pesticides currently in use are likely to cause the syndrome, even under extremely high exposures. There have been suggestions that OP compounds may have delayed effects following treatment for acute intoxication, after low-dose, long-term exposures, or following exposure to mixtures of OP insecticides and other chemicals *(45–47)*. Much remains to be done to define the precise mechanism(s) responsible for the neurotoxicities reported under these conditions, and any potential relationship to the classical OPIDN described earlier. A recent report indicated that antibodies to nervous-system proteins appeared in OP-exposed subjects *(48)*. Because the precise mechanism(s) and temporal sequence of events that lead to OPIDN are still unknown, the significance of this finding cannot be evaluated. Also, the lack of information on mechanisms makes treatment difficult when exposures occur and risk of the development of neuropathy is high.

The symbiotic relationship of NTE inhibition and OPIDN currently leaves many unanswered questions. The recent synthesis of potent and specific NTE inhibitors and the recent work on the molecular biology of NTE have the potential to define its possible role in the nervous system, both in the absence and presence of neuropathy-inducing OP compounds *(43,49)*.

OPIDN is expressed only in some long myelinated axonal fibers while others remain unaffected. Why this occurs is unknown. The relationship of the pathology to metabolic events in the whole neuron are at present undefined. Cell-culture systems have potential to provide models for such studies. Culture systems can be chosen in which NTE and acetylcholinesterase are inhibited in a manner similar to that seen in exposed animals (Fig. 4), especially when systems for activating protoxicants are included *(50,51)*.

Prevention is always likely to be better than treatment of OPIDN. The establishment of regulatory guidelines for OP compounds that permit risk to be based on biochemical, clinical, and morphological features of OPIDN will continue to be important in

protection of the public *(8).* Review and refinement of the guidelines will continue as more information becomes available on the mechanism(s) associated with this disorder.

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