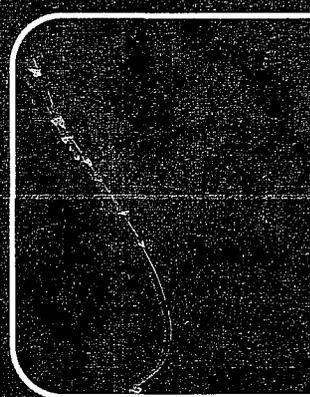


SEVENTH EDITION

Casarett & Doull's

Toxicology

The Basic Science of Poisons



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Table 8-24
Carcinogenic Factors Associated with Lifestyle

CHEMICAL(S)	NEOPLASM(S)
Alcohol beverage	Esophagus, liver, oropharynx, and larynx
Aflatoxins	Liver
Betel chewing	Mouth
Dietary intake (fat, protein, calories)	Breast, colon, endometrium, gallbladder
Tobacco smoking	Mouth, pharynx, larynx, lung, esophagus, bladder

Table 8-25
Occupational Human Carcinogens

AGENT	INDUSTRIAL PROCESS	NEOPLASMS
Asbestos	Construction, asbestos mining	Peritoneum, bronchus
Arsenic	Mining and smelting	Skin, bronchus, liver
Alkylating agents (methylchloro-ethamine hydrochloride and bis[chloromethyl]ether)	Chemical manufacturing	Bronchus
Benzene	Chemical manufacturing	Bone marrow
Benzidine, beta-naphthylamine	Dye and textile	Urinary bladder
Chromium and chromates	Tanning, pigment making	Nasal sinus, bronchus
Nickel	Nickel refining	Nasal sinus, bronchus
Polynuclear aromatic hydrocarbons	Steel making, roofing, chimney cleaning	Skin, scrotum, bronchus
Vinyl chloride monomer	Chemical manufacturing	Liver
Wood dust	Cabinet making	Nasal sinus
Beryllium	Aircraft manufacturing, electronics	Bronchus
Cadmium	Smelting	Bronchus
Ethylene oxide	Production of hospital supplies	Bone marrow
Formaldehyde	Plastic, textile, and chemical	Nasal sinus, bronchus
Polychlorinated biphenyls	Electrical-equipment production and maintenance	Liver

Table 8-26
Human Carcinogenic Chemicals Associated with Medical Therapy and Diagnosis

CHEMICAL OR DRUG	ASSOCIATED NEOPLASMS
Alkylating agents (cyclophosphamide, melphalan)	Bladder, leukemia
Azathioprine	Lymphoma, reticulum cell sarcoma, skin, Kaposi's sarcoma (?)
Chloramphenicol	Leukemia
Diethylstilbestrol	Vagina (clear cell carcinoma)
Estrogens	Liver cell adenoma, endometrium, skin
Phenacetin	Renal pelvis (carcinoma)
Phenytoin	Lymphoma, neuroblastoma
Thorotrast	Liver (angiosarcoma)

consumption contributes anywhere from 2 to 4% of cancers of the esophagus, liver, and larynx.

Poor diets whether high fat, low protein, high calories, or diets lacking in needed antioxidants and minerals account for anywhere from 10 to 70% of human cancers. Diet contaminated by molds such as *Aspergillus flavus* (which produces aflatoxin B1) have been linked epidemiologically to a higher incidence of liver cancer. It also appears that aflatoxin B1 exposure coupled with hepatitis B virus infection produces an increased incidence of liver cancer compared to aflatoxin B1 or hepatitis B exposure individually. Mold contaminated food stuffs have also been shown to produce nitroso compounds.

There is substantial evidence that over nutrition either through excess calories and/or high fat diets contribute to a number of human

cancers (Doll and Peto, 1981). In particular high fat and high calorie diets have been linked to breast, colon, and gall bladder cancer in humans. Diets poor in antioxidants and/or vitamins such as vitamin A and vitamin E probably also contribute to the onset of cancer. The method of cooking may also influence the production of carcinogens produced in the cooking process. Carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons are formed during broiling and grilling of meat. Acrylamide, a suspected human carcinogen has been found in fried foods at low concentrations.

A number of occupations have been associated with the development of specific cancers (Table 8-25). As noted earlier, the linkage between chimney sweepers who as young boys in England were exposed to polyaromatic hydrocarbons through constant exposure to soot, developed scrotal cancer. The linkage between occupational

behavior has not been conclusively determined, it has been suggested that degeneration of vestibular sensory hair cells is responsible (Llorens *et al.*, 1993).

Pathologic changes also follow administration of IDPN, most notably in large caliber axons, the primary target of neurotoxicity. The accumulation of neurofilaments in the proximal axon occurs, leading to swelling without degeneration in most animals (Gold, 2000). Quails deficient in neurofilaments demonstrate no swellings when administered IDPN, suggesting that the toxicity is due to a selective effect on neurofilaments (Mitsubishi *et al.*, 1993). These neurofilament swellings are similar to those observed in carbon disulfide or γ -diketones toxicity. Repeated exposure to IDPN leads to demyelination and onion bulb formation, and eventually can produce distal axonal atrophy due to a reduction in anterograde neurofilament transport to the distal axon (Clark *et al.*, 1980).

This impairment of axonal transport results from the disruption of the association between microtubules and neurofilaments by IDPN, causing neurofilament accumulation (Griffin *et al.*, 1983). This leads to complete disturbance of the cytoskeleton of the axon. Although unclear, the mechanism responsible for this interference is hypothesized to result from the direct alteration of neurofilament proteins by IDPN, possibly by changing their chemical properties and causing aggregation (Anderson *et al.*, 1991).

Acrylamide Acrylamide is a vinyl monomer used widely in water purification, paper manufacturing, mining, and waterproofing. It is also used extensively in biochemical laboratories, and is present in many foods prepared at high temperatures. Although it can be dangerous if not handled carefully, most toxic events in humans have been observed as peripheral neuropathies in factory workers exposed to high doses (Garland and Peterson, 1967; Kesson *et al.*, 1977; Collins *et al.*, 1989; Myers and Macun, 1991).

Early studies of acrylamide neuropathy revealed a distal axonopathy characterized by multiple axonal swellings (Spencer and Schaumburg, 1976). Although a single large dose is enough to produce toxicity, the process appears the same in multiple smaller doses, suggesting that acrylamide neurotoxicity is not due to an accumulation of the toxicant in the brain (Crofton *et al.*, 1996). Repeated dosing results in a more proximal axonopathy, in a "dying back" process. The first changes are seen in Pacinian corpuscles, followed by muscle spindles and the nerve terminal. These changes are caused by accumulations of neurofilaments at the nerve terminal. Paranodal swellings develop, leading to the retraction of myelin (Schaumburg *et al.*, 1974; Spencer and Schaumburg, 1974). A decrease in the number of synaptic vesicles and mitochondria at the nerve terminal is also characteristic, probably due to inhibition of retrograde and anterograde axonal transport (DeGrandchamp *et al.*, 1990; Padilla *et al.*, 1993; Harris *et al.*, 1994). Recently it has been observed that nerve terminal degeneration occurs prior to development of axonopathy, suggesting that this degeneration is the primary lesion (LoPachin *et al.*, 2002).

Many early studies investigating acrylamide neurotoxicity noted nerve terminal degeneration, but for three decades the distal axonopathy was believed to be the lesion responsible for neurologic symptoms (ataxia, numbness in extremities, etc.). However, in more recent studies, neurologic symptoms and nerve terminal degeneration were similarly observed in both short-term high dose and long-term low dose animals in the rat PNS, while axonal degeneration occurred only in low-dose studies subsequent to neurologic alteration (LoPachin *et al.*, 2002).

Organophosphorus (OP) Compounds OP compounds are used not only as insecticides and chemical warfare agents, but also as chemical intermediates, flame retardants, fuel additives, hydraulic fluids, lubricants, pharmaceuticals, and plasticizers. The OP insecticides and nerve agents are designed to inhibit acetylcholinesterase (AChE), thereby causing accumulation of acetylcholine in cholinergic synapses resulting in cholinergic toxicity and death (Thompson and Richardson, 2004). However, apart from the insecticides, nerve agents, and some of the pharmaceuticals, OP compounds produced for other applications often have little or no anti-AChE activity (Richardson, 2005).

Some OP compounds, such as tri-*o*-cresyl phosphate (TOCP), are neuropathic and can cause a severe sensorimotor central peripheral distal axonopathy called OP compound-induced delayed neurotoxicity (OPIDN) without inducing cholinergic poisoning. This condition is also referred to as a delayed neuropathy or delayed polyneuropathy (OPIDP) (Lotti and Moretto, 2005). However, *neuropathy* usually connotes peripheral nerve disease, whereas OPIDN also involves degeneration of ascending and descending spinal cord tracts (Richardson, 2005).

An OPIDN epidemic of massive proportions occurred during Prohibition in the United States, when Jamaica Ginger extract (Ginger Jake), a popular source of alcohol, was adulterated with TOCP. Another outbreak occurred in Morocco where olive oil was contaminated with TOCP. Human cases have also occurred after exposure to certain formerly used OP insecticides, such as EPN [*O*-ethyl-*O*-4-nitrophenyl phenylphosphonothionate] and leprophos [*O*-(4-bromo-2,5-dichlorophenyl)-*O*-methyl phenylphosphonothionate] (Lotti and Moretto, 2005).

Many OP compounds are hydrophobic and readily enter the NS. If the parent compound and/or metabolites have suitable reactivity, they can phosphorylate neural target proteins, such as various serine hydrolases (Casida and Quistad, 2005). When the principal target is acetylcholinesterase (AChE), cholinergic toxicity can ensue, either because of suprathreshold levels of inhibition or inhibition plus aging (Fig. 16-5). A substantial level of AChE inhibition on its own is sufficient to produce cholinergic toxicity and death. When *aging* of inhibited AChE also occurs (net loss of a ligand from the phosphorus of the OP-enzyme conjugate, leaving a negatively charged phosphoryl moiety attached to the active site), the qualitative nature of the toxicity does not change. Instead, the inhibited AChE becomes intractable to reactivation, rendering therapy with oximes, such as 2-pralidoxime methiodide (2-PAM) ineffective (Fig. 16-5) (Thompson and Richardson, 2004).

When the principal target is neuropathy target esterase (neurotoxic esterase, NTE), OPIDN can result only if both suprathreshold (>70%) inhibition occurs *and* the inhibited enzyme undergoes aging. Thus, in the case of NTE and OPIDN, inhibition alone is insufficient to precipitate toxicity. It appears that the biochemical lesion is not simply a blockade of the active site. Instead, axonopathy is triggered by specific chemical modification of the NTE protein (Fig. 16-6). Neuropathic (aging) inhibitors of NTE include compounds from the phosphate, phosphonate, and phosphoramidate classes of OP compounds (Richardson, 1992; Kropp *et al.*, 2004) (Fig. 16-7).

Certain NTE inhibitors, including members of the phosphinate, carbamate, and sulfonylfluoride classes, do not age and do not cause OPIDN (Fig. 16-7). However, pretreatment with a nonaging NTE inhibitor prevents OPIDN from occurring after a challenge dose of a neuropathic (aging) NTE inhibitor. It has been proposed that these nonaging compounds protect against OPIDN by blocking the