Parkinson* & (*icide*, fumigant*, organophosph*, organochlorine*, pyrethrin*, pyrethroid*, cyclodiene*, wood preservative*, carbamate*, dithiocarbamate*, alkylated phosphate*, grain,
atrazine, carbaryl, carbon disulfide, chlorpyrifos, DDE, deltamethrin, dichlorvos, dieldrin, dimethoate, diquat, diphenyl, dithiocarb, glyphosate, heptachlor, hexachlorobenzene, HCH*, hexachlorocyclohexane, lindane, malathion, maneb, paraquat, permethrin, rotenone, soman, triadimefon, zineb)
[& no results for: DEET, sumithrin, tetramethrin]

Aguirre JA, Cintra A, Hillion J, Narvaez JA, Jansson A, Antonelli T, Ferraro L, Rambert FA, Fuxe K. 1999. A stereological study on the neuroprotective actions of acute Modafinil treatment on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced nigral lesions of the male black mouse. Neurosci Lett 275(3):215-218.
Abstract: The effect of an acute administration of the vigilance-promoting drug modafinil ((+/-)(diphenyl-methyl)-sulfinyl-2 acetamide; Modiodal) on the nigrostriatal dopamine system was studied after damage induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) by means of immunohistochemistry for tyrosine hydroxylase (TH) and a stereological method. MPTP (40 mg/kg) reduced from 24 380 +/- 902 to 13 501 +/- 522 and from 37 868 +/- 3300 to 20 568 +/- 1270, respectively, the number of TH immunoreactive (IR) and non-TH IR nigral neurons. Go-administration of Modafinil restored to normal the number of these neuronal populations. MPTP treatment induced also a reduction in the volume of TH IR neurons, which was counteracted by Modafinil administration. The data provide morphological evidence, based on unbiased stereological analysis, for a potential neuroprotective role of Modafinil, not only in dopaminergic neurons, but also with a similar magnitude in the non-DA nerve cell population of the substantia nigra after MPTP lesion. These results suggest that Modafinil has a neuroprotective role in the substantia nigra via a still undefined mechanism in which a crucial role of DA uptake blockade should be excluded. Modafinil may therefore have a therapeutic potential in neurodegenerative processes such as those occurring in Parkinson's disease. (C) 1999 Elsevier Science Ireland Ltd. All rights reserved.

Aigaki T, Kaneuchi T, Matsuo T, Seong KH, Togawa T. 2003. Genetic bases of oxidative stress resistance and life span in Drosophila. Journal of Clinical Biochemistry and Nutrition 34(2):77-83.
Abstract: The fruit fly, Drosophila melanogaster, is an excellent model system for the study of complex biological processes including aging. Through genetic manipulation of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, the roles of these enzymes in oxidative stress resistance and life span determination were established. Transgenic flies overexpressing the enzyme peptide methionine sulfoxide reductase A (MSRA) have been shown to live longer and are more resistant to paraquat-induced oxidative stress. It has been also demonstrated that mutations in genes involved in the insulin/insulin-like growth factor (IGF) pathway (IGF receptor, chico, dFOXO) affected life span and sensitivity to various stresses. We have conducted a conditional gene misexpression

screen to identify genes, whose overexpression in adult stages extends life span. Among 13 genes whose functions are known or suggested, six genes were found to be related to stress resistance or redox balance (DmGST2, hsp26, sra, and Drosophila homologs of mammalian TRX, GILT, and POSH). We recently established a method for the efficient measurement of oxidative stress resistance in Drosophila, using a commercially available activity monitor. The method is suitable for the screening of oxidative stress resistance-related genes using a large number of mutagenized fly lines.

Akhmedova SN, Yakimovsky AK, Schwartz EI. 2001. Paraoxonase 1 Met-Leu 54 polymorphism is associated with Parkinson's disease. J Neurol Sci 184(2): 179-182.
Abstract: Two up-to-date known paraoxonase 1 (PON1) polymorphisms (GIn-Arg 191 and Leu-Met 54) affect the hydrolysis of toxic oxons and might intensify effects of pollutants, organophosphates and other environmental chemicals in development of Parkinson's disease (PD). We reported previously that PON1 Gln-Arg 191 polymorphism did not influence on the susceptibility to PD. In the present study we have investigated the PON1 Leu-Met 54 polymorphism in 117 patients with sporadic idiopathic PD. A new approach for Leu-Met 54 polymorphism genotyping has been developed. We have showed the frequency of the Met 54 allele of PON1 to be significantly increased in patients with PD compared with the controls (chi (2)=8.63, df=1, P<0.003). The relative risk of PD in the Met 54 allele carriers has been estimated to be 2.3 fold higher than in homozygotes for the L allele. Moreover it appeared to be even 5.15 higher in the subgroup of patients with early-onset PD. We suggest that the Met 54 allele may be considered to be an independent risk factor for PD. This mutation could probably cause PON1 impaired metabolism of environmental neurotoxins and might be responsible for neurodegeneration. <(c)> 2001 Published by Elsevier Science B.V.

Akpinar MB, Erdogan H, Sahin S, Ucar F, Ilhan A. 2005. Protective effects of caffeic acid phenethyl ester on rotenone-induced myocardial oxidative injury. Pestic Biochem Physiol 82(3):233-239.
Abstract: Rotenone, an insecticide, causes toxicity through inhibition of mitochondrial electron transport chain at complex I and oxidative injury to the tissues. The aim of the present study was to determine in vivo effects of rotenone on myocardium and cardio-protective effects of caffeic acid phenethyl ester (CAPE), an antioxidant agent, against rotenone toxicity in rats. The rats were divided into three groups: untreated control, rotenone (2.5 mg/kg/day for 60 days, i.p.) and rotenone + CAPE groups. CAPE was administrated i.p. 10 ltmol/kg/day for 62 days started two days before first dose rotenone injection. The malondialdehyde, nitric oxide levels and xanthine oxidase activity of rotenone group was significantly higher than control and rotenone + CAPE groups (to < 0.05). However, catalase activity in the rotenone group was decreased in comparison with the other groups (p < 0.05). The superoxide dismutase activity of rotenone group was insignificantly decreased compared to the others. In conclusion, rotenone caused lipid peroxidation in myocardial tissue and CAPE

treatment prevented this rotenone-induced lipid peroxiclation in rats. CAPE might be a cardio-protective agent against myocardial toxicities. (c) 2005 Elsevier Inc. All rights reserved.

Akundi RS, Macho A, Munoz E, Lieb K, Bringmann G, Clement HW, Hull M, Fiebich BL. 2004 . 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline-induced apoptosis in the human neuroblastoma cell line SK-N-SH. J Neurochem 91 (2):263-273.
Abstract: Trichloroethylene, a common industrial solvent and a metabolic precursor of chloral hydrate, occurs widely in the environment. Chloral hydrate, which is also used as a hypnotic, has been found to condense spontaneously with tryptamine, in vivo, to give rise to a highly unpolar 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) that has a structural analogy to the dopaminergic neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Earlier studies have revealed the relative permeability of the molecule through the blood-brain barrier and its ability to induce Parkinson-like symptoms in rats. In this study, we report that TaClo induces an apoptotic pathway in the human neuroblastoma cell line, SK-N-SH, involving the translocation of mitochondrial cytochrome c to the cytosol and activation of caspase 3. TaClo-induced apoptosis shows considerable differences from that mediated by other Parkinson-inducing agents such as MPTP, rotenone and manganese. Although it is not clear if the clinically administered dosage of chloral hydrate or the relatively high environmental levels of trichloroethylene could lead to an onset of Parkinson's disease, the spontaneous in vivo formation of TaClo and its pro-apoptotic properties, as shown in this report, should be considered.

Al-Dirbashi O, Kuroda N, Menichini F, Noda S, Minemoto M, Nakashima K. 1998. Enantioselective high-performance liquid chromatography with fluorescence detection of methamphetamine and its metabolites in human urine. Analyst 123(11):2333-2337.
Abstract: A simple, rapid and highly sensitive high-performance liquid chromatographic method with fluorescence detection for determining the enantiomers of methamphetamine and its major metabolites, amphetamine and p-hydroxymethamphetamine, in urine samples was developed. Using a newly developed reagent for amines, namely, 4-(4,5-diphenyl-1H-imidazol-2-yl)benzoyl chloride, six enantiomers were derivatized under mild conditions (i.e., 10 min at room temperature, pH 9.0) and separated isocratically on a cellulose tris(3,5-dimethylphenylcarbamate) coated silica gel column following a pre-separation on an ODS column within 42 min, and the effluent was monitored at 440 nm (lambda(ex) 330 nm). Calibration curves for these derivatives using spiked human urine were linear in the range 0.05-100 mu mol dm(-3) with correlation coefficients greater than or equal to 0.999. The detection limits at a signal-to-noise ratio of 3 were 2.8-8.8 fmol per 5 mu l injection. The relative standard deviations of within- (n = 6) and between-day (n = 5) variations were less than or equal to 7.4%. The method was successfully applied to discriminate between (S)-(+)-methamphetamine and its corresponding metabolites found in abusers' urine and their

antipodes in a sample taken from a Parkinsonian patient on selegiline (Deprenyl) therapy.

Alam M, Mayerhofer A, Schmidt WJ. 2004. The neurobehavioral changes induced by bilateral rotenone lesion in medial forebrain bundle of rats are reversed by L-DOPA. Behav Brain Res 151(1-2):117-124.
Abstract: Rotenone (an inhibitor of mitochondrial complex 1) has been proposed as a model of Parkinson's disease (PD) as it induces nigrostriatal degeneration associated with alpha-synuclein inclusions. So far, only peripherally administered rotenone has been used as a model of PD. There has not been any investigation on the neurobehavioral changes induced by bilateral lesions of dopaminergic neurons by rotenone in rats. In the present study, rotenone (3 mug) was administered bilaterally stereotaxically into the medial forebrain bundle (MFB) to produce parkinsonian symptoms. Behavioural and biochemical data showed a strong increase in catalepsy, a decrease in locomotor activity and a significant depletion of dopamine levels in the striatum as compared to sham-lesioned animals. If the locomotor deficits are caused by the depletion of dopaminergic neurons, then L-DOPA should counteract motor deficits because L-DOPA therapy reverses mostly all motor deficits in human Parkinsonian patients. To examine the effectiveness of L-DOPA in reversing the motor deficit in rats, two different doses of L-DOPA (5 and 10 mg/kg) in combination with the peripheral amino acid decarboxylase inhibitor benserazide were daily administrated intraperitonially for a period of 31 days lesioned animals. L-DOPA plus benserazide counteracted catalepsy dose-dependently and increased locomotor activity. The results indicate that rotenone infused into the MFB destroys dopaminergic neurons, induces pakinsonian symptoms that are reversed by the clinically effective anti-parkinsonian drug L-DOPA. Therefore, sterotaxically infused rotenone may be useful for screening drugs for the treatment of PD. (C) 2003 Elsevier B.V. All rights reserved.

Alam M, Schmidt WJ. 2002. Rotenone destroys dopaminergic neurons and induces parkinsonian symptoms in rats. Behav Brain Res 136(1):317-324.
Abstract: Rotenone (an inhibitor of mitochondrial NADH dehydrogenase, a naturally occurring toxin and a commonly used pesticide) appears to reproduce the neurochemical, neuropathological and behavioural feature of Parkinson's disease (PD) in the rat. In this study, rotenone was administrated on a daily basis systemically by intraperitoneal injection of two different doses: 1.5 mg/kg (low dose) and 2.5 mg/kg (moderate dose), over a period of 2 months. This treatment caused depletion of dopamine in the posterior striatum (CPu) and prefrontal cortex and also reduced tyrosine hydroxylase-immunoreactivity in CPu. Behavioural experiments showed dose-dependent catalepsy in the two treatment groups of rats. Data from this study indicate that in rats rotenone is capable of causing degeneration of dopaminergic neurons and induction of parkinsonian symptoms. It is concluded that the causal mechanisms of neuronal degeneration implicate a complex I deficiency in the aetiology of rotenone-induced and perhaps in some cases of sporadic PD. (C) 2002

Alam M, Schmidt WJ. 2004. L-DOPA reverses the hypokinetic behaviour and rigidity in rotenone-treated rats. Behav Brain Res 153(2):439-446.
Abstract: Peripherally and locally administered rotenone (an inhibitor of mitochondrial complex 1) has been proposed as a model of Parkinson's disease (PD) as it induces nigrostriatal degeneration associated with alpha-synuclein inclusions. If rotenone-induced symptoms represent a model of PD, than they should be counteracted by L-DOPA. To answer this question, rats were treated with rotenone 2.5 mg/kg over 48 days. Behavioural data showed a strong increase in catalepsy, a decrease in locomotor activity and biochemical data showed a significant depletion of dopamine levels in the striatum (Cpu) and substantia nigra in rotenone treated animals compared to vehicle. To examine the effectiveness Of L-DOPA in reversing the motor deficit in rats, a dose Of L-DOPA (10 mg/kg) in combination with the peripheral amino acid decarboxylase inhibitor benserazide were daily administrated intraperitonially for a period of 10 days in the rotenone-treated rats. This treatment counteracted catalepsy and increased locomotor activity and number of rearings but decreased inactive sitting. In this animal model (rotenone model), catalepsy tests and motor activities showed that the clinically used anti-parkinsonian drug L-DOPA substitutes rotenone-induced dopamine (DA) deficiency. (C) 2004 Elsevier B.V. All rights reserved.

Alam M, Schmidt WJ. 2004. Mitochondrial complex I inhibition depletes plasma testosterone in the rotenone model of Parkinson's disease. Physiology & Behavior 83(3):395-400.
Abstract: Age-related depletion of testosterone may increase the brain's vulnerability to parkinsonian- or Alzheimer's-like neurodegenerative disorders. In rats, rotenone, a mitochondrial complex I inhibitor, causes specific nigral dopaminergic neurodegeneration producing parkinsonian symptoms. In this study, rotenone was administered on a daily basis (2 mg/kg i.p.) to two groups of rats, over a period of 30 and 60 days, respectively. In order to contribute towards the validation of the rotenone rat model, the changing level of the peripheral sex steroid hormone, testosterone, which would also mimic those found in Parkinson's disease (PD) patients, was evaluated. Parallel to this, prolactin, luteinizing hormone (LH), the nonsexual steroid thyroid-stimulating hormone, and the corticosterone hormone levels in the peripheral blood plasma were measured to show whether other hormones have also been affected by complex I inhibition. The rotenone treatment caused a decrease of testosterone level in the peripheral blood plasma. There were no differences in the thyroid hormone and prolactin but increases in leutinizing hormone and corticosterone were observed. Data from this study indicate that rotenone depleted the sex steroid hormone which is preferentially produced in the periphery, e.g., adrenal gland and testis. In conclusion, because a decrease in testosterone levels is also one of the comorbidities which are found in male PD patients, our results indicate that the rotenone model mimics PD symptoms not only on a neuronal and behavioral level, but also on the testosterone levels. (C) 2004 Elsevier Inc. All rights

reserved.

Albers JW, Berent S, Garabrant DH, Giordani B, Schweitzer SJ, Garrison RP, Richardson RJ. 2004. The effects of occupational exposure to chlorpyrifos on the neurologic examination of central nervous system function: A prospective cohort study. J Occup Environ Med 46(4):367-378.
Abstract: Questions persist about adverse effects such as impaired cognition and attention, incoordination, spasticity, or Parkinsonism from chronic, low-level exposures to organophosphate (OP) compounds. In a prospective cohort study, we evaluated chlorpyrifos-manufacturing workers and a referent group on 2 occasions, I year apart, to determine whether occupational exposure to chlorpyrifos produced clinically evident central nervous system (CNS) dysfunction. Chlorpyrifos subjects had significantly higher TCP excretion and lower average BuChE activity than referents in a range in which physiological effects on B-esterases exist. Few subjects had neurologic symptoms or signs, and there were no significant group differences in terms of signs at baseline or second examinations. Chronic chlorpyrifos exposure produced no clinical evidence of cortical, pyramidal tract, extrapyramidal, or other CNS dysfunction among chlorpyrifos subjects compared with referents, either at baseline or after I year of additional chlorpyrifos exposure.

Allain P, Krari N. 1991. Diethyldithiocarbamate, copper and neurological disorders. Life Sci 48(3):291-299.

Allam MF, Del Castillo AS, Navajas RF. 2005 Mar. Parkinson's disease risk factors: genetic, environmental, or both? Neurol Res 27(2):206-8.
Abstract: Perhaps one of the most important questions posed by the neurobiology of aging concerns the pathogenic mechanisms in Parkinson's disease (PD). Recently, it was suggested that exposure to pesticides could be the main cause of PD. Another study reported that the environmental endotoxin, lipopolysaccaride produced by Salmonella minnesota, might be a risk factor for PD. An alternative explanation is the genetic component, which has been suggested to be an important risk factor. Epidemiological studies have identified a positive family history of Parkinson as one of the most important risk factors for the disease. However, these studies neither examined nor reviewed the medical records of the family members. The twin study stated that the major factors in the etiology of PD are non-genetic. Meanwhile, epidemiological studies from China have shown that the prevalence of PD is much lower than in the Caucasian population, explained by the low frequency of cytochrome P-450 CYP2D6 debrisoquine hydroxylase gene polymorphism. The etiology of idiopathic PD is still a question for scientists, and calls for further research, especially with the growing proportion of elderly and the rising incidence of PD worldwide. Future research for PD risk factors should consider that multiple interactions occur in PD, resulting in a complex trait, which includes genetic, acquired, and environmental components.

Allam MF, Del Castillo AS, Navajas RFC. 2003. Parkinson's disease risk factors. Rev Neurol 36(8):749-755.

Abstract: Aims. In this review we present and discuss the main risk factors (RF) for Parkinson's disease (PD) reported by epidemiological and biochemical research. Methods. The most frequently mentioned RF are: 1. Age: PD is not a pathological condition that is restricted to the elderly, although most people who suffer from it are over 60 Years of age; 2. Sex: in most epidemiological studies there are no differences to be found in prevalence of PD according to sex; 3. Genetic: no gene has been identified as being responsible for idiopathic PD. Nevertheless, family antecedents of PD have. been identified as RF; 4. Craneoencephalic trauma: this factor can have a systematic bias, since patients seek an explanation for their illness and remember any head injury as its possible cause; 5. Neurotoxins: a great deal of research was focused on the relation between PD and direct or indirect exposition to compounds such as MPTP, used in pesticides; 6. Antioxidants: it is thought that if ingested in sufficiently high quantities, either as part of the diet or in the form of supplements, they might reduce the risk of PD or slow down its progress; 7. Smoking: several studies have shown a negative relation, while other studies found no significant relation. Conclusions. There are several RF for PD, although no single decisive triggering factor has been found to date. Future research must consider the hypothesis of a multifactor aetiology and take into account the interaction between genetic and environmental factors.

Allam MF, Del Castillo AS, Navajas RFC. 2005. Parkinson's disease risk factors: genetic, environmental, or both? Neurol Res 27(2):206-208.
Abstract: Perhaps one of the most important questions posed by the neurobiology of aging concerns the pathogenic mechanisms in Parkinson's disease (PD). Recently, it was suggested that exposure to pesticides could be the main cause of PD. Another study reported Et the environmental endotoxin, lipopolysaccaride produced by Salmonella minnesota, m be a risk factor for PD. An alternative explanation is the genetic component, which has been suggested to be an important risk factor. Epidemiological studies have identified a positive family history of Parkinson as one of the most important risk factors for the disease. However, these studies neither examined nor reviewed the medical records of the family members. The twin study stated that the major factors in the etiology of PD are non-genetic, Meanwhile, egidemiological studies from China have shown that the prevalence of PD is much lower than in the Caucasian copulation, explained by the low frequency of cytochrome P-450 CYP2D6 debrisoquine hydroxylase gene polymorphism. The etiology idiopathic PD is still a question for scientists and calls for further research, especially WINtofeigrowing proportion of elderly and the rising incidence of PD worldwide. Future research for PD risk factors should consider that multiple interactions occur in PD, resulting in a complex trait, which includes genetic, acquired, and environmental components.

Andersen JK. 2003. Paraquat and iron exposure as possible synergistic environmental risk factors in Parkinson's disease. Neurotoxicity Research 5 (5):307-313.

Anderson JJ, Bravi D, Ferrari R, Davis TL, Baronti F, Chase TN, Dagani F. 1993.

No evidence for altered muscle mitochondrial-function in parkinsons-disease. J Neurol Neurosurg Psychiatry 56(5):477-480.
Abstract: Recent reports indicate that reductions in mitochondrial respiratory chain function occur in substantia nigra, platelets, and muscle from patients with Parkinson's disease. To confirm and further characterise the presence of a generally distributed mitochondrial defect, mitochondrial metabolism was evaluated in muscle obtained from subjects with Parkinson's disease and from normal controls. Oxygen consumption rates in muscle mitochondria represented by complex I, complexes II-III, or complex IV did not differ between the two groups. Likewise, activities of rotenone sensitive NADH cytochrome c reductase, succinate cytochrome c reductase, or cytochrome oxidase in muscle mitochondria were not significantly different between Parkinsonian and control subjects. These findings fail to provide support for a generalised defect in mitochondrial function in Parkinson's disease but do not exclude an abnormality in respiratory function confined to the substantia nigra.

Andre C, Truong TT, Robert JF, Guillaume YC. 2005. Effect of metals on herbicides-alpha-synuclein association: A possible factor in neurodegenerative disease studied by capillary electrophoresis. Electrophoresis 26(17):3256-3264.
Abstract: The aggregation of a-synuclein in the dopaminergic neurons of the substantia nigra is a critical step in the Parkinson's disease (PD). The etiology of the disease is unknown but recent epidemiological and experimental studies have renewed interest in the hypothesis that environmental factors, especially herbicides and metals, have a role on the pathogenesis of PD. For the first time, the association constants of a-synuclein with five herbicides have been calculated using a capillary electrophoresis (CE) method. In addition, the effect of a number of metals on this binding has been investigated. It appears that the herbicides preferentially bind to a partially folded intermediate conformation of a-synuclein induced by manganese, aluminium, cadmium, copper and zinc. Then, metal increases the synuclein-herbicide association. However, this study shows contrasting actions with the antibiotic rifampicin and magnesium addition leading to a decrease of the alpha-synuclein-herbicide interaction even if other metals are present in the bulk solvent. Considering epidemiological studies, all these results suggest an underlying molecular basis for PD and related body diseases.

ANDRE MJ, STIERNET P. 1950 Apr 22. [New case of Parkinsonism due probably to carbon disulfide poisoning.]. Presse Med 58(25):437-8.

[Anon]. 2000. Global update - Pesticide could be linked with Parkinson's disease. Neuroreport 11(18):A16.

[Anon]. 2001. Relationship between rotenone use in fisheries management and Parkinson's disease. Fisheries 26(3):36-37.

[Anon]. 2001. Scientists suggest a link between rotenone and Parkinson's

disease. South Med J 94(3):364.

Antkiewicz-Michaluk L, Karolewicz B, Romanska I, Michaluk J, Bojarski AJ, Vetulani J. 2003. 1-Methyl-1,2,3,4-tetrahydroisoquinoline protects against rotenone-induced mortality and biochemical changes in rat brain. Eur J Pharmacol 466(3):263-269.
Abstract: The effect of single and multiple administration of the neurotoxic pesticide, rotenone, and the potentially neuroprotective compound, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ), on the concentration of dopamine and its metabolites (homovanillic acid-HVA, 3,4-dihydroxyphenylacetic acid-DOPAC, and 3-methoxytyramine-3-MT)) in three brain areas was studied by high-performance liquid chromatography (HPLC) with electrochemical detection in Wistar rats. The rate of dopamine catabolism in the striatum along the N-oxidative and O-methylation pathways was assessed by calculation of the ratio of dopamine metabolites to dopamine. In addition, the effect of rotenone on mortality and general behavior of rats was investigated. We have found that the neurotoxic pesticide, rotenone, administered in a single dose (12 mg/kg s.c.) did not produce evident behavioral or biochemical effects. In contrast, repeated administration of rotenone in doses (12 15 mg/kg) causing abnormalities in general behavior, produced considerable mortality and dramatic increases in dopamine metabolism, which may be ascribed to an increase in the oxidative pathway. Interestingly, it depressed the concentration of the extracellular dopamine metabolite, 3-MT. These behavioral and biochemical changes were effectively counteracted by administration of 1MeTIQ before each dose of rotenone. In summary, we demonstrated that multiple systemic rotenone injections are strongly toxic, and induce alterations of cerebral dopamine metabolism, and that 1MeTIQ may be considered as a potential protective agent against environmental factors affecting the function of the dopaminergic system. (C) 2003 Elsevier Science B.V. All rights reserved.

Antkiewicz-Michaluk L, Wardas J, Michaluk J, Romanska I, Bojarski A, Vetulani J. 2004. Protective effect of 1-methyl-1,2,3,4-tetrahydroisoquinoline against dopaminergic neurodegeneration in the extrapyramidal structures produced by intracerebral injection of rotenone. International Journal of Neuropsychopharmacology 7(2):155-163.
Abstract: The aim of this paper was to investigate whether rotenone, a pesticide causing experimental parkinsonism, causes direct damage to dopaminergic structure when injected intracerebrally and whether this action may be prevented by peripheral administration of 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ), an endogenous compound with anti-dopaminergic activity. Male Wistar rats were injected unilaterally into the median forebrain bundle with 2 mug rotenone, and received 1MeTIQ, 50 mg/kg i.p. 1 h before and then daily for 21 d. To compare the effect of intracerebral and peripheral treatment, rotenone was also given once or for 7 d in a dose of 10 mg/kg s.c. Dopamine, serotonin and their metabolites were assessed by HPLC in the substantia nigra and striatum. While a single subcutaneous rotenone dose did not produce any change in striatal dopamine metabolism, the multiple treatments resulted in changes

suggesting a shift in the metabolism towards oxidative desamination and reduction of O-methylation. In contrast to systemic injections, intracerebral-administered rotenone produced a decrease in dopamine and its metabolites content in the striatum (dopamine decrease by 70%) and substantia nigra (dopamine decrease by 35 %), without affecting the serotonin system. As those changes were observed 21 d after the injection of rotenone, they suggest a durable neurotoxic effect. The treatment with 1MeTIQ strongly reduced the fall of striatal dopamine concentration. The data suggest that rotenone given peripherally affects metabolic processes in dopaminergic neurons, and this seems to result from its neurotoxic action, which may be observed after an intracerebral injection. 1MeTIQ is able to counteract the damaging action of rotenone and seems to be a potential neuroprotective agent.

Arima H, Sobue K, So MH, Morishima T, Ando H, Katsuya H. 2003. Transient and reversible parkinsonism after acute organophosphate poisoning. J Toxicol Clin Toxicol 41(1):69-72.
Abstract: Parkinsonism is a rare complication in patients with organophosphate poisoning. To date there have been two cases of transient parkinsonism after acute and severe cholinergic crisis, both of which were successfully treated using amantadine, an anti-parkinsonism drug. We report on an 81-year-old woman who was admitted for the treatment of acute severe organophosphate poisoning. Although acute cholinergic crisis was treated successfully with large doses of atropine and 2-pyridine aldoxime methiodide (PAM), extrapyramidal manifestations were noticed on hospital day 6. The neurological symptoms worsened, and the diagnosis of parkinsonism was made by a neurologist on hospital day 9. Immediately, biperiden (5 mg), an anti-parkinsonism drug, was administered intravenously, and her symptoms markedly improved. From the following day, biperiden (5 mg/day) was given intramuscularly for eight days. Subsequently, neurological symptoms did not relapse, and no drugs were required. Our patient is the third case of parkinsonism developing after an acute severe cholinergic crisis and the first case successfully treated with biperiden. Patients should be carefully observed for the presence of neurological signs in this kind of poisoning. If present, an anti-parkinsonism drug should be considered.

Aruoma OI. 2003. Methodological considerations for characterizing potential antioxidant actions of bioactive components in plant foods. Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis 523(Sp. Iss. Si):9-20.
Abstract: The study of free radicals and antioxidants in biology is producing medical revolution that promises a new age of health and disease management. From prevention of the oxidative reactions in foods, pharmaceuticals and cosmetics to the role of reactive oxygen species (ROS) in chronic degenerative diseases including cancer, autoimmune, inflammatory, cardiovascular and neurodegenerative (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, Downs syndrome) and aging challenges continue to emerge from difficulties associated with methods used in evaluating antioxidant actions in vivo. Our interest

presently is focused on development of neurodegeneration models based on the integrity of neuronal cells in the central nervous system and how they are protected by antioxidants when challenged by neurotoxins as well as Fenton chemistry models based on the profile of polyunsaturated fatty acids (PUFAs) for the assessment of antioxidant actions in vivo. Use continues to be made of several in vitro analytical tools to characterise the antioxidant propensity of bioactive compounds in plant foods and supplements. For example, the oxygen radical absorbance capacity (ORAC), ferric reducing antioxidant power (FRAP), total oxidant scavenging capacity (TOSC), the deoxyribose assay, assays involving oxidative DNA damage, assays involving reactive nitrogen intermediates (e.g. ONOO-), Trolox equivalent antioxidant capacity (TEAC) and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. There is need to agree governance on in vitro antioxidant methods based on an understanding of the mechanisms involved. Because some of the assays are done in non-physiological pH values, it is impossible to extrapolate the results to physiological environment. The consensus of opinion is that a mix of these tools should be used in assessing the antioxidant activities in vitro. The proof of bio-efficacy must emanate from application of reliable in vivo models where markers of baseline oxidative damage are examined from the standpoint of how they are affected by changes in diet or by antioxidant supplements. 

Ascherio A, O'reilly EJ, Weisskopf MG, Mccullough ML, Chen HL, Schwarzschild MA, Calle EE, Thun MJ. 2005. Prospective study of pesticide exposure and risk of Parkinson's disease. Neurology 64(6):A282.

Aschner M. 2000. Manganese: Brain transport and emerging research needs. Environ Health Perspect 108:429-432.
Abstract: Idiopathic Parkinson's disease (IPD) represents a common neurodegenerative disorder. An estimated 2% of the U.S. population, age 65 and older, develops IPD. The number of IPD patients will certainly increase over the next several decades as the baby-boomers gradually step into this high-risk age group, concomitant with the increase in the average life expectancy. While many studies have suggested that industrial chemicals and pesticides may underlie [PD, its etiology remains elusive. Among the toxic metals, the relationship between manganese intoxication and IPD has long been recognized. The neurological signs of manganism have received close attention because they resemble several clinical disorders collectively described as extrapyramidal motor system dysfunction, and in particular, IPD and dystonia. However, distinct dissimilarities between IPD and manganism are well established, and it remains to be determined whether Mn plays an etiologic role in IPD. It is particularly noteworthy that as a result of a recent court decision, methylcyclopentadienyl Mn tricarbonyl (MMT) is presently available in the United States and Canada for use in fuel, replacing lead as an antiknock additive. The impact of potential long-term exposure to low levels of MMT combustion products that may be present in emissions from automobiles has yet to be fully evaluated. Nevertheless, it should be pointed out that recent studies with Various environmental modeling approaches in the

Montreal metropolitan (where MMT has been used for more than 10 years) suggest that airborne Mn revels were quite similar to those in areas where MMT was not used. These studies also show that Mn is emitted from the tail pipe of motor vehicles primarily as a mixture of manganese phosphate and manganese sulfate. This brief review characterizes the Mn speciation in the blood and the transport kinetics of Mn into the central nervous system, a critical step in the accumulation of Mn within the brain, outlines the potential susceptibility of selected populations (e.g., iron-deficient) to Mn exposure, and addresses future research needs for Mn.

Bachurin SO, Shevtzova EP, Lermontova NN, Serkova TP, Ramsay RR. 1996. The effect of dithiocarbamates on neurotoxic action of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) and on mitochondrial respiration chain. Neurotoxicology 17(3-4):897-903.
Abstract: The neurotoxin MPTP induces in human and in some laboratory animals parkinsonism-like neurological disorder, biochemically characterized by selective and irreversible decrease of dopamine content in striatum. The terminal step in the mechanism of neurotoxic action of MPTP is the inhibition of mitochondrial respiratory chain by pyridinium metabolite (MPP+) resulting in energy depletion and nervous cells death. Earlier it was shown that some chemical compounds, in particular diethyldithiocarbamate (DTC), can potentiate MPTP neurotoxicity. In the present work we have studied the influence of DTC derivatives on MPTP neurotoxic effect in vivo and on MPP+ inhibition of mitochondrial respiration (both on intact mitochondria and on submitochondrial particles) in vitro. It was revealed that DTC alone change mitochondrial membrane state by respiratory chain uncoupling and inhibition. DTC and MPP+ mutually potentiate inhibition of electron Transport as well. The combined effect of DTC plus MPP+ action on mitochondria respiration reflects the sum of reciprocally leveling and potentia ting factors and can explain the order of efficacy of MPTP-neurotoxicity potentiation in vivo in series of close DTC derivatives. (C) 1996 Intox Press, Inc.

Bachurin SO, Tkachenko SE, Lermontova NN. 1991. Pyridine derivatives: structure-activity relationships causing parkinsonism-like symptoms. Rev Environ Contam Toxicol 122:1-36.
Abstract: In recent years, sufficient evidence has surfaced to implicate low-molecular-weight organic compounds in certain known neurological disorders. At this time, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is considered the compound capable of inducing conditions most similar to idiopathic parkinsonism in clinical, biochemical, and histopathological characteristics. Substances containing MPTP-like fragments are used as herbicides, drugs and intermediates in the synthesis of many heterocyclic compounds. The mechanistic study of toxic MPTP action has enabled development of criteria for appraising potential parkinsonogenic properties of similar chemical structures. Key features of MPTP action include the following: 1. Ability to pass through the blood-brain barrier (BBB). 2. Enzymatic biotransformation to the neuroactive form (pyridine metabolites). 3. Transfer to neurons via a neuromediator reuptake system. 4. Action on intracellular targets. This review discusses

data concerning the effects of metabolite structure on the major steps in the neurotropic action mechanism of MPTP-like compounds. Special attention is focused on the key steps defining the selectivity of MPTP's neuronal action, i.e., the activation step caused by monoamine oxidase (MAO) and interaction with the dopamine (DA) reuptake system. Most structural MPTP analogs (including certain pesticide preparations) used in our experiments and described in the literature exhibit no degenerative MPTP-like properties. This is probably related to the fact that each consecutive stage in the MPTP neurotoxicity mechanism makes rather stringent demands on metabolite structure. The number of structures which concurrently meet the requirements of all the processes is finite. This, however, does not invalidate the hypotheses concerning the ecotoxic nature of idiopathic parkinsonism. Possible ecotoxins may have only a partial, presymptomatic effect which, however, promotes age-related neurodegenerative processes and accelerates development of parkinsonism. This concept necessitates designing special tests of the possible neurotoxic properties of compounds found in the environment which may be functional MPTP analogs.

Bagetta G, Corasaniti MT, Iannone M, Nistico G, Stephenson JD. 1992. Production of limbic motor seizures and brain-damage by systemic and intracerebral injections of paraquat in rats. Pharmacology & Toxicology 71(6):443-448.
Abstract: The behavioural and neuropathological effects of both systemic and intrahippocampal injections of paraquat dichloride (1,1'-dimethyl 4,4'-bipyridinium dichloride) were studied in rats. Paraquat (0.1-1.0 mumol) injected into the dorsal hippocampus, produced limbic motor seizures within a few minutes of injection followed by neuronal damage in the CA1 and CA3 pyramidal cell layers, pyriform cortex, dentate granule cell layer and in the hilus fascia dentata at 24 hr (n=9 rats). A smaller dose of paraquat (10 nmol) was ineffective. The effects of intrahippocampal injections of paraquat (1 mumol) were prevented by administering it together with atropine (50 nmol; n=6 rats) or by giving it 60 min. after MK 801 (0.3 mg.kg-1 intraperitoneally). Systemic injections of paraquat (20-100 mg.kg-1) also produced forelimb clonus and rearing in 10 out of 15 animals. Neuronal cell death was found 24 hr later in 9 of these rats and was restricted to the pyriform cortex, the brain region with the highest concentrations of paraquat. Atropine (150 mg.kg-1 intraperitoneally given 60 min. previously) completely prevented the motor seizures but cell death still occurred in 2 of the 6 animals tested. In conclusion, both systemic and intrahippocampal injections of paraquat produced behavioural excitation accompanied 24 hr later by brain damage and antagonist studies suggested involvement of muscarinic and NMDA receptors in the neurotoxic mechanism.

Bahat-Stroomza M, Gilgun-Sherki Y, Offen D, Panet H, Saada A, Krool-Galron N, Barzilai A, Atlas D, Melamed E. 2005. A novel thiol antioxidant that crosses the blood brain barrier protects dopaminergic neurons in experimental models of Parkinson's disease. Eur J Neurosci 21(3):637-646.
Abstract: It is believed that oxidative stress (OS) plays an important role in the loss of dopaminergic nigrostriatal neurons in Parkinson's disease (PD)

and that treatment with antioxidants might be neuroprotective. However, most currently available antioxidants cannot readily penetrate the blood brain barrier after systemic administration. We now report that AD4, the novel low molecular weight thiol antioxidant and the N-acytel cysteine (NAC) related compound, is capable of penetrating the brain and protects neurons in general and especially dopaminergic cells against various OS-generating neurotoxins in tissue cultures. Moreover, we found that treatment with AD4 markedly decreased the damage of dopaminergic neurons in three experimental models of PD. AD4 suppressed amphetamine-induced rotational behaviour in rats with unilateral 6-OHDA-induced nigral lesion. It attenuated the reduction in striatal dopamine levels in mice treated with 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP). It also reduced the dopaminergic neuronal loss following chronic intrajugular administration of rotenone in rats. Our findings suggest that AD4 is a novel potential new neuroprotective drug that might be effective at slowing down nigral neuronal degeneration and illness progression in patients with PD.

Bahiga LM, Kotb NA, El-Dessoukey EA. 1978 Jun. Neurological syndromes produced by some toxic metals encountered industrially or environmentally. Z Ernahrungswiss 17(2):84-8.
Abstract: Toxic metals encountered industrially or environmentally may produce the following syndromes: 1) Peripheral neuropathy: which is mainly sensory in arsenic and entirely motor with inorganic lead, organophosphorus compounds and tallium produce a mixed form of peripheral neuropathy. 2) Encephalopathy: usually with lead poisoning where ataxia and hemiplegia or optic atrophy may occur. 3) Optic neuritis: transient or permanent impairment of vision in arsenic poisoning and blurring of vision followed by field fedects with thallium poisoning. 4) Cerebellar disturbances: in the form of ataxia in organic mercury. 5) Parkinsonism: extrapyramidal signs occurs in manganese poisoning shown as mask face and rigidity of muscles. 6) Mental changes: as acute psychosis in organic lead and erethism in organic mercury.

Baldereschi M, Di Carlo A, Vanni P, Ghetti A, Carbonin P, Amaducci L, Inzitari D. 2003 . Lifestyle-related risk factors for Parkinson's disease: a population-based study. Acta Neurol Scand 108(4):239-244.
Abstract: Objectives - To investigate the association of major lifestyle-related risk factors with the prevalent cases of Parkinson's disease (PD) identified by the Italian Longitudinal Study on Aging. Methods - A total of 5632 individuals randomly selected from the population registers of eight centers were screened for parkinsonism using both a questionnaire and a neurologic examination. Screened positives underwent a structured clinical work-up for the diagnosis of parkinsonism and parkinsonism subtypes. Results - We identified 113 prevalent cases of PD. Age, male gender, and pesticide-use license were significantly related to PD. Heavy smoking was inversely related to PD. Age (OR = 1.1; 95% CI, 1.06 - 1.15) and pesticide-use license ( OR = 3.7; 95% CI, 1.6 - 8.6) kept their significant correlation with the disease in the multivariate analysis to adjust for all the variables under investigation. Multivariate analyses were made for men

and women separately: pesticide exposure was positively associated with PD only in men. Conclusions - Pesticide exposure might represent a candidate for environmental factors involved in PD.

Baldi I, Brochard P, Mohammed-Brahim B, Rolland P, Salamon R. 1999. Methods for retrospective assessment of occupational exposure to pesticides. Rev Epidemiol Sante Publique 47(2):165-174.
Abstract: The extensively growing use of pesticides in the last decades has led to great improvements in agriculture but also to threats for human health. Studying long term effects to assess individual exposures encounters difficulties in exposure assessment. This article summarizes retrospective,methods for assessing occupational exposures to pesticides currently used in epidemiological studies, Questionnaires, environmental and biological monitoring constitute direct assessment of exposure, in an individual approach. But the validity of questionnaires is often poor and the metrology rarely reflects past exposures. Some indirect measures have been used together with job exposure matrices. To establish dose-response relationships is important to quantify the risk, but needs accurate exposure assessment based on quantitative indexes.

Baldi I, Cantagrel A, Lebailly P, Tison F, Dubroca B, Chrysostome V, Dartigues JF, Brochard P. 2003. Association between Parkinson's disease and exposure to pesticides in southwestern France. Neuroepidemiology 22(5):305-310.
Abstract: A case-control study was performed in southwestern France in order to assess the relationship between pesticide exposure and Parkinson's disease (PD) in the elderly. During the period from 1997 to 1999, 84 cases were recruited together with 252 population-based controls. Experts in occupational health reviewed job codes and provided pesticide exposure levels, making it possible to calculate cumulated exposure lifelong for individuals. Environmental pesticide exposure was considered in relation to the place of residence. A positive association was found with occupational pesticide exposure (odds ratio = 2.2, 95% confidence interval 1.1-4.3) in conditional logistic multiple regression analysis taking into account age, sex, educational level and smoking; however, no clear dose relationship was found. Our results support the hypothesis of an association between occupational pesticide exposure and PD and point to the need to investigate the role of fungicides, for which toxicological hypotheses exist. Copyright (C) 2003 S. Karger AG, Basel.

Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. 2003. Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol 157(5):409-414.
Abstract: The authors investigated the hypothesis that exposure to pesticides could be related to central nervous system disorders in a prospective cohort study of 1,507 French elderly (1992-1998). Lower cognitive performance was observed in subjects who had been occupationally exposed to pesticides. In men, the relative risks of developing Parkinson's disease and Alzheimer's disease for occupational exposure assessed by a job exposure matrix were 5.63 (95% confidence interval: 1.47, 21.58) and 2.39 (95% confidence interval: 1.02, 5.63),

respectively, after confounding factors were taken into account. No association was found with having a primary job in agriculture or with environmental pesticide exposure, nor was an association found in women. These results suggest the presence of neurologic impairments in elderly persons who were exposed occupationally to pesticides.

Baldi I, Mohammed-Brahim BM, Brochard P, Dartigues JF, Salamon R. 1998. Long-term effects of pesticides on health: review of current epidemiologic knowledge. Rev Epidemiol Sante Publique 46(2):134-142.
Abstract: The use of pesticides has extensively grown in the last decades, regardless of the economic level of the countries. This led to great improvements in agriculture but also a threat for human health. Short term effects are quite well known through approval procedures for pesticides. On the other hand, long term effects are nor properly assessed. A review of epidemiologic knowledge is presented here. Epidemiologic studies on pesticides have found associations with long-term effects on health mainly in three fields : cancer (especially hematological cancer), neurotoxic effects (polyneuropathy, neurobehavioral hazards, Parkinson's disease), and reproductive disorders (infertility, birth defects, adverse pregnancy outcomes, perinatal mortality). These conclusions have been obtained despite difficulties in exposition assessment due to the retrospective nature of the studies. But the continuous development of pesticide use in agriculture, and also in domestic environment, emphasizes the need for epidemiologic studies on long-term effects of pesticides relying on accurate exposure assessment.

Bandopadhyay R, Kingsbury AE, Cookson MR, Reid AR, Evans IM, Hope AD, Pittman AM, Lashley T, Canet-Aviles R, Miller DW, Mclendon C, Strand C, Leonard AJ, Abou-Sleiman PM, Healy DG, Ariga H, Wood NW, De Silva R, Revesz T, Hardy JA, Lees AJ. 2004. The expression of DJ-1 (PARK7) in normal human CNS and idiopathic Parkinson's disease. Brain 127:420-430.
Abstract: Two mutations in the DJ-1 gene on chromosome1p36 have been identified recently to cause early-onset, autosomal recessive Parkinson's disease. As no information is available regarding the distribution of DJ-1 protein in the human brain, in this study we used a monoclonal antibody for DJ-1 to map its distribution in frontal cortex and substantia nigra, regions invariably involved in Parkinson's disease. Western blotting of human frontal cortex showed DJ-1 to be an abundant protein in control, idiopathic Parkinson's disease, cases with clinical and pathological phenotypes of Parkinson's disease with R98Q polymorphism for DJ-1, and in progressive supranuclear palsy (PSP) brains. We also showed that DJ-1 immunoreactivity (IR) was particularly prominent in astrocytes and astrocytic processes in both control and Parkinson's disease frontal cortex, whereas neurons showed light or no DJ-1 IR. Only occasional Lewy bodies (LBs), the pathological hallmarks of Parkinson's disease, showed faint DJ-1 IR, localized to the outer halo. In preclinical studies we showed that DJ-1 is expressed in primary hippocampal and astrocyte cultures of mouse brain. By 2D gel analysis we also showed multiple pI isoforms for DJ-1 ranging between 5.5-6.6 in both control and Parkinson's disease brains, whilst exposure of M17 cells to the oxidizing agent paraquat was manifested as a

shift in pI of endogenous DJ-1 towards more acidic isoforms. We conclude that DJ-1 is not an essential component of LBs and Lewy neurites, is expressed mainly by astrocytes in human brain tissue and is sensitive to oxidative stress conditions. These results are consistent with the hypothesis that neuronal-glial interactions are important in the pathophysiology of Parkinson's disease.

Bao L, Avshalumov MV, Rice ME. 2005. Partial mitochondrial inhibition causes striatal dopamine release suppression and medium spiny neuron depolarization via H2O2 elevation, not ATP depletion. J Neurosci 25(43): 10029-10040.
Abstract: Mitochondrial dysfunction is a potential causal factor in Parkinson's disease. We show here that acute exposure to the mitochondrial complex I inhibitor rotenone (30-100 nM; 30 min) causes concentration-dependent suppression of single-pulse evoked dopamine (DA) release monitored in real time with carbon-fiber microelectrodes in guinea pig striatal slices, with no effect on DA content. Suppression of DA release was prevented by the sulfonylurea glibenclamide, implicating ATP-sensitive K+ (K-ATP) channels; however, tissue ATP was unaltered. Because K-ATP channels can be activated by hydrogen peroxide (H2O2), as well as by low ATP, we examined the involvement of rotenone-enhanced H2O2 generation. Confirming an essential role for H2O2, the inhibition of DA release by rotenone was prevented by catalase, a peroxide-scavenging enzyme. Striatal H2O2 generation during rotenone exposure was examined in individual medium spiny neurons using fluorescence imaging with dichlorofluorescein (DCF). An increase in intracellular H2O2 levels followed a similar time course to that of DA release suppression and was accompanied by cell membrane depolarization, decreased input resistance, and increased excitability. Extracellular catalase markedly attenuated the increase in DCF fluorescence and prevented rotenone-induced effects on membrane properties; membrane changes were also largely prevented by flufenamic acid, a blocker of transient receptor potential (TRP) channels. Thus, partial mitochondrial inhibition can cause functional DA denervation via H2O2 and K-ATP channels, without DA or ATP depletion. Furthermore, amplified H2O2 levels and TRP channel activation in striatal spiny neurons indicate potential sources of damage in these cells. Overall, these novel factors could contribute to parkinsonian motor deficits and neuronal degeneration caused by mitochondrial dysfunction.

Barbeau A, Dallaire L, Buu NT, Poirier J, Rucinska E. 1985 Oct 21. Comparative behavioral, biochemical and pigmentary effects of MPTP, MPP+ and paraquat in Rana pipiens. Life Sci 37(16):1529-38.
Abstract: We demonstrate that injections of 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), 1-methyl-4-phenyl-pyridinium ion (MPP+) and Paraquat (PQ+) produce in Rana Pipiens different behavioral, biochemical and skin pigmentation changes. MPTP causes in frogs the main symptoms of Parkinsonism (rigidity, akinesia and tremor) and it darkens the skin of animals. It also decreases brain and, less so, adrenal medulla dopamine. These effects are blocked by Pargyline. MPP+ causes the same symptoms

but more rapidly. In contrast, skin pigmentation is clearly lightened. Brain and particularly adrenal dopamine reserves are nearly abolished. Pargyline increases these effects. Paraquat, in a cumulative fashion, eventually causes the same behavioral changes and a slight increase in pigmentation. It initially produces an increase in brain and adrenal dopamine concentrations, but later a significant dopamine concentration decrease. Pargyline potentiates these long term effects, blocks the dopamine increase, but reverses the PQ+ effect upon melanin, producing the same depigmentation as MPP+ alone.

Barbeau A, Roy M, Bernier G, Campanella G, Paris S. 1987 Feb. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. Can J Neurol Sci 14(1):36-41.
Abstract: We make use of the unique combination of a homogeneous genetic and racial origin in the rural population of Quebec and the facilities of free and universal access to medical care, to study the distribution of the prevalence of Parkinson's disease in the 9 rural hydrographic regions of the Province. Through 3 different methods of ascertainment, confirmed by two control probes, we demonstrate that the prevalence of Parkinson's disease is of uneven distribution within rural areas. We further investigated the characteristics of the regions of high prevalence. These regions which are predominantly agricultural and areas of intensive market gardening were also the areas with the highest use of pesticides.

Barbosa ER, Da Costa MDL, Bacheschi LA, Scaff M, Leite CC. 2001. Parkinsonism after glycine-derivate exposure. Mov Disord 16(3):565-568.
Abstract: This 54-year-old man accidentally sprayed himself with the chemical agent glyphosate, a herbicide derived from the amino acid glycine. He developed disseminated skin lesions 6 hours after the accident. One month later, he developed a symmetrical parkinsonian syndrome. Two years after the initial exposure to glyphosate, magnetic resonance imaging revealed hyperintense signal in the globus pallidus and substantia nigra, bilaterally, on T2-weighted images. Levodopa/benserazide 500/125 mg daily provided satisfactory clinical outcome.

Barlow BK, Lee DW, Cory-Slechta DA, Opanashuk LA. 2005. Modulation of antioxidant defense systems by the environmental pesticide maneb in dopaminergic cells. Neurotoxicology 26(1):63-75.
Abstract: A lack of evidence supporting a role of heritability in the development of idiopathic Parkinson's disease (PD) has implicated exposures to environmental contaminants in the disease etiology. Epidemiological and clinical studies, as well as animal models of the Pl) phenotype, have consistently linked agrichemical exposure with dopaminergic (DAergic) damage, particularly through oxidative stress mechanisms. Maneb (MB) is a dithiocarbamate (DTC),fungicide that has specifically been implicated to have adverse effects on dopatnine (DA) systems, but the role MB plays in modulating the oxidative state of DAergic cells has not previously been described. Since glutathione (GSH) is a major cellular antioxidant, it was hypothesized that exposure to MB would disrupt this system. The current study primarily utilized the PC12 cell line, which

displays a catecholaminergic phenotype. Low concentrations of MB (50-1000 ng/ml) had little effect on cell viability, as measured by LDH release. These same concentrations, however led to increases in GSH and its oxidized form, GSSG. Effects on viability and GSH were correlated to a primary mesencephalic culture system. Furthermore, these effects were markedly differentfrom those observed with the classical oxidative stressor and pesticide, paraquat (PQ). To determine how MB would affect cells in which antioxidant systems were compromised, PC12 cells were treated with L-buthionine-(SR)-sulfoximine (BSO) to deplete cellular GSH, followed by treatment with MB. Results suggest that following an insult to the GSH antioxidant system, MB can act as an additional insult to the system and prevent the normal recovery of those defenses. Altered protein levels of heme oxygenase-1 (HO- 1) further indicated an oxidative stress response elicited by MB in PC12 cells. DAergic neurons, as a population, are inherently vulnerable to oxidative stress, and the disruption of antioxidant systems by the fungicide MB may contribute to the neurodegeneration of these cells, especially with concurrent exposures to other environmentally relevant oxidative stressors, such as PQ. (C) 2004 Elsevier Inc. All rights reserved.

Barlow BK, Richfield EK, Cory-Slechta DA, Thiruchelvam M. 2004. A fetal risk factor for Parkinson's disease. Dev Neurosci 26(1):11-23.
Abstract: A lack of strong evidence for genetic heritability of idiopathic Parkinson's disease (PD) has focused attention on environmental toxicants in the disease etiology, particularly agrichemicals. PD is associated with advanced age, but it is unclear whether specific neuronal damage could result from insults during development. This study hypothesized that prenatal exposure to pesticides would disrupt the development of the nigrostriatal dopamine (DA) system and enhance its vulnerability to dopaminergic neurotoxicant exposures later in life. Pregnant C57BL/6J mice were treated on gestational days 10-17 with saline or the pesticides maneb (MB, 1 mg/kg) or paraquat (PQ, 0.3 mg/kg). When offspring were evaluated in adulthood, there were no significant effects of prenatal MB or PQ exposure on locomotor activity. Subsequently, offspring were treated for 8 consecutive days with saline, MB (30 mg/kg), or PQ (5 mg/kg). One week after the last exposure, only males exposed to prenatal MB and adulthood PQ showed significant reductions in locomotor activity (95%) and changes in striatal neurochemistry. Stereological assessment of the substantia nigra pars compacta (SNpc) and ventral tegmental area correspondingly confirmed selective dopaminergic-neuron loss in SNpc. The lack of changes in other exposure groups suggests a specificity to the sequence of exposures as well as gender specificity. These results suggest that prenatal exposure to MB produces selective, permanent alterations of the nigrostriatal dopaminergic system and enhances adult susceptibility to PQ exposure. This study implicates a role for developmental neurotoxicant exposure in the induction of neurodegenerative disorders such as PD. Copyright (C) 2004 S. Karger AG, Basel.

Barlow BK, Thiruchelvam MJ, Bennice L, Cory-Slechta DA, Ballatori N, Richfield EK. 2003. Increased synaptosomal dopamine content and brain

concentration of paraquat produced by selective dithiocarbamates. J Neurochem 85(4):1075-1086.
Abstract: Exposure to pesticides may be a risk factor for Parkinson's disease based on epidemiologic data in humans, animal models and in vitro studies. Different dithiocarbamate pesticides potentiate the toxicity of both 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and paraquat in mouse models of Parkinsonism by an unknown mechanism. This study examined the effects of commercially used dithiocarbamates on [(3) H]dopamine transport in striatal synaptosomal vesicles and on the concentration of [(14) C]paraquat in vivo in mice. Different ethylenebis-dithiocarbamates and diethyl-dithiocarbamate increased dopamine accumulation in synaptosomes, whereas dimethyl-dithiocarbamate and methyl-dithiocarbamate did not. Increased dopamine accumulation in synaptosomes was dose dependent and was related to the carbon backbone of these molecules. The dithiocarbamates that increased accumulation of dopamine did not alter the influx of dopamine, but rather delayed the efflux out of synaptosomes. These same dithiocarbamates also increased the tissue content of [(14) C]paraquat in vivo by a mechanism that appeared to be distinct from the dopamine transporter. There was a consistent relationship between the dithiocarbamates that increased synaptosomal accumulation of dopamine and tissue content of paraquat, with those previously demonstrated to enhance paraquat toxicity in vivo . These results suggest that selective dithiocarbamates may alter the kinetics of different endogenous and exogenous compounds to enhance their neurotoxicity.

Bashkatova V, Alam M, Vanin A, Schmidt WJ. 2004. Chronic administration of rotenone increases levels of nitric oxide and lipid peroxidation products in rat brain. Exp Neurol 186(2):235-241.
Abstract: The complex I inhibitor rotenone is a neurotoxin that has been proposed to induce Parkinson-like degeneration. As the mechanisms of rotenone toxicity are not fully understood, the present study addresses the question of whether rotenone induces NO production and lipid peroxidation-like products, that is, thiobarbituric acid reactive substances (TBARS). Rotenone at a dose of 1.5 mg kg(-1) ip was administered to rats daily for 10, 20; 30, and 60 days, and NO and TBARS were measured in the frontal cortex and in the striatum. On the 1st and 10th day, there were no increases in NO and TBARS levels, after 20 days, the NO and TBARS levels were increased in the striatum. After 30 and 60 days, NO and TBARS levels were increased in striatum and frontal cortex. Behaviorally, on days 30 and 60, the rats exhibited akinesia and rigidity in the catalepsy test. These results show that chronic administration of rotenone over a long period is capable of increasing NO and TBARS in the cortex and striatum and mimics Parkinson's disease (PD)-like behavioral symptoms that are akinesia and rigidity in rats. (C) 2004 Elsevier Inc. All rights reserved.

Basma AN, Heikkila RE, Saporito MS, Philbert M, Geller HM, Nicklas WJ. 1992. 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine-induced toxicity in pc12 cells is enhanced by preventing glycolysis. J Neurochem 58(3): 1052-1059.

Abstract: The effects of 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine (2'Et-MPTP), 1-methyl-4-(2'-ethylphenyl)pyridinium (2'Et-MPP+), and the classic complex 1 inhibitor, rotenone, on toxicity as well as on rates of glucose use and lactate production were studied using the pheochromocytoma PC12 cell line. PC12 cells are neoplastic in nature and have a high rate of glycolysis accompanied by a large production of lactate and a low use of glucose carbon through the Krebs cycle. 1-Methyl-4-phenylpyridinium (MPP+) and analogues such as 2'Et-MPP+ are actively accumulated by mitochondrial preparations in vitro and block NADH dehydrogenase of complex 1. This blockade results in biochemical sequelae that are ultimately cytotoxic. In this study, untreated PC12 cells used glucose and concomitantly accumulated lactate in a time-dependent manner at all concentrations of glucose studied. Treatment with 50-mu-M 2'Et-MPP+ or 50 nM rotenone increased both rates significantly, indicating a shift toward increased glycolysis. Cell death caused by the neurotoxins was also time and concentration dependent and markedly enhanced by glucose depletion in the medium. The increase in 2'Et-MPTP-induced toxicity in low glucose-supplemented cells was not due to an increase in pyridinium formation from the tetrahydropyridine, but rather to the lack of glucose for glycolysis. Moreover, inhibition of glycolysis with 2-deoxyglucose or iodoacetic acid also enhanced the lethality of the neurotoxins to the cells. The data in this study provide additional support to the hypothesis that 2'Et-MPP+ or related analogues act to kill cells by inhibiting mitochondrial respiration. Furthermore, these findings support the hypothesis that the ability of 2'Et-MPTP or its analogues to induce toxicity is dependent on the relative contributions of glycolysis and mitochondrial oxidation to the energy needs of a particular cell or model system.

Behari M, Srivastava AK, Das RR, Pandey RM. 2001. Risk factors of Parkinson's disease in Indian patients. J Neurol Sci 190(1-2):49-55.
Abstract: Epidemiological data on risk factors of Parkinson's disease (PD) are not available from India. In a case control study, we investigated environmental and genetic risk factors in the etiology of idiopathic Parkinson's disease. Three hundred seventy-seven patients of Parkinson disease (301 men, 76 women, mean +/- SD age 56.78 +/- 11.08 years) and equal number of age matched (+/-3 years) neurological controls (271 men, 106 women, mean +/- SD age 56.62 +/- 11.17 years) were included in the study. Conditional logistic regression model was used to determine the risk factors of PD. We found that male gender, family history of Parkinson's disease, past history of depression of up to 10-year duration and well water drinking of more than 10-year duration were significantly associated with occurrence of Parkinson's disease, whereas tobacco smoking of up to 20-year duration and exposure to pets had protective effect. However, tobacco smoking of more than 20-year duration, well water drinking of up to 10-year duration, vegetarian dietary habit, occupation involving physical exertion, rural living, farming, exposure to insecticides, herbicides, rodenticides, alcohol intake and family history of neurodegenerative diseases had no significant correlation with occurrence

of PD in the patient population studied. Results of our study support the hypothesis of multifactorial etiology of PD with environmental factors acting on a genetically susceptible host. (C) 2001 Elsevier Science B.V. All rights reserved.

Bell IR, Amend D, Kaszniak A, Schwartz GE, Peterson JM, Stini WA, Miller JW, Selhub J. 1995. Trait shyness in the elderly - evidence for an association with parkinsons-disease in family members and biochemical correlates. J Geriatr Psychiatry Neurol 8(1 ):16-22.
Abstract: The emergence of potential treatments to slow the progression of idiopathic Parkinson's disease (PD) has increased the need for early identification of persons at risk. Although considered controversial, some prior studies indicate that PD patients may have premorbid histories of greater trait introversion or shyness as well as increased rates of disorders associated with shyness (e.g., anxiety, affective disorders, and irritable bowel syndrome). Essential features of trait shyness include (a) inhibited and avoidant behaviors and (b) physiological hyperreactivity to the novel or unfamiliar. In parallel, (a) depression in PD patients is associated with increased harm avoidance (a possible serotonergic function), and (b) PD patients have premorbid and comorbid decreases in novelty-seeking (a possible dopaminergic function). Taken together, previous research suggests the following hypotheses: (1) given evidence for marked heritability of shyness, shy elderly should report higher rates of PD in their family members than would nonshy elderly; and (2) shy elderly without PD should exhibit psychological and biologic characteristics similar to those reported in PD. Two groups, representing the top 27% (n = 37) and bottom 31% (n = 43) of scores on a standardized shyness scale, were drawn from a larger cohort of 138 older adults (ages 50-90) living in an active retirement community. Seventeen percent of the shy versus 2% of the nonshy reported PD in a family member or self (P <.05). Shy elderly were significantly more anxious (P < .01) and depressed (P < .05) than were the nonshy. Shy subjects rated themselves significantly higher on feeling ill from the odor of environmental chemical (pesticide, car exhaust, paint, perfume, new carpet) than did the nonshy group. In a separate study of non-PD patients, depressed elderly with self-reported childhood shyness in themselves (n = 7) showed higher levels than did depressed elderly without childhood shyness (n = 7) of plasma L-cysteine (P = .05), the sulfurated amino acid previously shown to be elevated in PD patients, as well as of post-dexamethasone plasma cortisol (P < .05). The findings support the hypotheses and suggest the need for additional investigation of the neurobiology of trait shyness as a possible risk factor for PD.

Bell IR, Schwartz GE, Amend D, Peterson JM, Kaszniak AW, Miller CS. 1994. Psychological characteristics and subjective intolerance for xenobiotic agents of normal young-adults with trait shyness and defensiveness - a parkinsonian-like personality type. J Nerv Ment Dis 182(7):367-374.
Abstract: The present study examines the psychological characteristics and self-reported responses to xenobiotic agents such as tobacco smoke and pesticide of normal young adults with personality traits similar to those claimed for Parkinsonian patients. Previous research, though controversial,

has suggested that persons with idiopathic Parkinson's disease (PD) have premorbid personality traits that may include shyness and repressive defensiveness. Other epidemiological evidence indicates that PD patients may have premorbidly increased prevalence of anxiety, affective, and/or somatoform disorders; decreased rates of smoking and alcohol consumption; and elevated exposure to herbicides or pesticides. A total of 783 college students enrolled in an introductory psychology course completed the Cheek-Buss Scale (shyness), the Marlowe-Crowne Social Desirability Scale (defensiveness), Symptom Checklist 90 (revised), the Mastery Scale, a health history checklist, and rating scales for frequency of illness from alcohol and 10 common environmental chemicals. Subjects were divided into four groups on the basis of above- versus below-median scores on the Cheek-Buss and Marlowe-Crowne scales (persons high in shyness and defensiveness, those high only in shyness, those high only in defensiveness, and those low in both shyness and defensiveness). The group high in shyness but low in defensiveness had the highest, whereas the group low in shyness but high in defensiveness had the lowest, total scores on the SCL-90-R; the two shyest groups were lowest in sense of mastery. Similar to PD, the group high in both shyness and defensiveness overall reported the least number of smokers (10% vs. 19% in those high only in shyness, 17% in those high only in defensiveness, and 28% in those low in both traits, $p < .001$); differences within women largely accounted for this finding. Subjects higher in shyness and/or defensiveness rated themselves higher in frequency of illness from a small amount of alcohol than did those who were low in both shyness and defensiveness. The group who was high in both shyness and defensiveness tended to report the highest frequency of illness from pesticide as well as other xenobiotic odors (e.g., newsprint). Taken together with previous research, the findings suggest that certain young adults high in shyness, and especially those also high in defensiveness, may be among the subset of the population at increased risk for PD later in life.

Bell IR, Schwartz GE, Peterson JM, Amend D, Stini WA. 1993. Possible time-dependent sensitization to xenobiotics - self-reported illness from chemical odors, foods, and opiate drugs in an older adult-population. Arch Environ Health 48(5):315-327.

Abstract: The present paper summarizes key features of time-dependent sensitization (TDS) in neuropharmacology (progressive amplification of behavioral, neuronal, endocrine, and/or immune responses to repeated intermittent exposures to an environmental agent or cross-sensitizing agents) as a possible model for cacosmia (subjective sense of feeling ill from low levels of environmental chemical odors) in nonindustrial and industrial populations; and extends previous cacosmia research in nonpatient populations to an elderly sample. This study examined the symptom and psychological profiles of 263 older adults (aged 60-90 y, 71% women, 29% men); 57% reported that at least one chemical and 17% reported that at least four of five chemicals (pesticide, automobile exhaust, paint, new carpet, perfume) made them feel ill. Cacosmia ratings correlated weakly and negatively with age ($r = -0.19$, $p = .001$) over the

whole sample. Cacosmia correlated significantly with self-reported illness from foods that may mobilize or generate opioid peptides (wheat, dairy, eggs) ($r = 0.32$, $p < .0001$) and with illness from opiate drugs ($r = 0.23$, $p < .0001$). When the sample was divided into four cells on the basis of above- versus below-median total chemical-induced illness score (CI) and total food-induced illness score (FI), the high CI and high FI, high CI only, and high FI only groups had more frequent indigestion, and the high CI group had more frequent difficulty concentrating than the groups below median for illness from both chemicals and foods (NOILL), even after co-varying for age and anxiety. The most cacosmic subjects noted higher prevalence of physician-diagnosed allergies and irritable bowel than did noncacosmic subjects. In contrast with previous young adult cohort studies, the older illness groups did not differ with regard to sex distribution, depression, shyness, or repressive defensiveness. When considered with prior surveys of young adults, the present findings are consistent with the presence of previously established, time-dependent sensitization to multiple xenobiotic agents in susceptible individuals for whom psychological variables do not explain the symptom of cacosmia. If cacosmia is a symptom of TDS, then the neuropharmacology literature suggests the possibility of excitatory amino acid, hypothalamic-pituitary-adrenal axis, dopaminergic, and/or opioid involvement. Prospective studies with objective measures testing the possible induction of TDS to specific chemicals are indicated.

Ben-Shlomo Y. 1997. The epidemiology of Parkinson's disease. Baillieres Clin Neurol 6(1):55-68.
Abstract: Epidemiological research has confirmed that Parkinson's disease (PD) is found throughout the world and increases exponentially with age. Few good-quality data on the temporal incidence of PD are available, although both mortality and incidence data suggest that the disease may be less common today in younger age groups. Differences in prevalence between identical ethnic groups in different countries support the role of an environmental factor. Any postulated factor must be found commonly in developed countries, among which there appears to be little difference in incidence or prevalence rates. A wide variety of aetiological agents have been considered from infectious, toxic and other exposures. The most robust finding is that non-smokers have a greater risk of disease, although the reason for this is unclear and may relate to differences in pre-morbid personality. Pesticides and head injuries also show consistently elevated risk but are prone to biased measurement. Dietary anti-oxidants require further evaluation. Future research needs to improve on current limited methods of exposure measurement and to attempt more novel designs to overcome bias. More attention should be made on examining what factors determine prognosis and using epidemiological and qualitative methods to determine the needs of patients with PD.

Benmoyal-Segal L, Vander T, Shifman S, Bryk B, Ebstein R, Marcus EL, Stessman J, Darvasi A, Herishanu Y, Friedman A, Soreq H. 2005. Acetylcholinesterase/paraoxonase interactions increase the risk of insecticide-induced Parkinson's disease. FASEB J 19(1).

Abstract: Exposure to agricultural insecticides, together with yet incompletely understood predisposing genotype/ phenotype elements, notably increase the risk of Parkinson's disease. Here, we report findings attributing the increased risk in an insecticide-exposed rural area in Israel to interacting debilitating polymorphisms in the ACHE/PON1 locus and corresponding expression variations. Polymorphisms that debilitate PON1 activity and cause impaired AChE overproduction under anticholinesterase exposure were strongly overrepresented in patients from agriculturally exposed areas, indicating that they confer risk of Parkinson's disease. Supporting this notion, serum AChE and PON1 activities were both selectively and significantly lower in patients than in healthy individuals and in carriers of the risky polymorphisms as compared with other Parkinsonian patients. Our findings suggest that inherited interactive weakness of AChE and PON1 expression increases the insecticide-induced occurrence of Parkinson's disease.

Benmoyal-Segal L, Vander T, Shifman S, Bryk B, Ebstein RP, Marcus EL, Stessman J, Darvasi A, Herishanu Y, Friedman A, Soreq H. 2005 Mar. Acetylcholinesterase/paraoxonase interactions increase the risk of insecticide-induced Parkinson's disease. FASEB J 19(3):452-4.
Abstract: Exposure to agricultural insecticides, together with yet incompletely understood predisposing genotype/phenotype elements, notably increase the risk of Parkinson's disease. Here, we report findings attributing the increased risk in an insecticide-exposed rural area in Israel to interacting debilitating polymorphisms in the ACHE/PON1 locus and corresponding expression variations. Polymorphisms that debilitate PON1 activity and cause impaired AChE overproduction under anticholinesterase exposure were strongly overrepresented in patients from agriculturally exposed areas, indicating that they confer risk of Parkinson's disease. Supporting this notion, serum AChE and PON1 activities were both selectively and significantly lower in patients than in healthy individuals and in carriers of the risky polymorphisms as compared with other Parkinsonian patients. Our findings suggest that inherited interactive weakness of AChE and PON1 expression increases the insecticide-induced occurrence of Parkinson's disease.

Benzi G, Curti D, Pastoris O, Marzatico F, Villa RF, Dagani F. 1991. Sequential damage in mitochondrial complexes by peroxidative stress. Neurochem Res 16(12):1295-1302.
Abstract: The biochemical characteristics of the electron transfer chain are evaluated in purified non-synaptic ("free") mitochondria from the forebrain of 60-week-old rats weekly subjected to peroxidative stress (once, twice, or three times) by the electrophilic prooxidant 2-cyclohexene-1-one. The following parameters are evaluated: (a) content of respiratory components, namely ubiquinone, cytochrome b, cytochrome c1, cytochrome c; (b) specific activity of enzymes, namely citrate synthase, succinate dehydrogenase, rotenone-sensitive NADH: cytochrome c reductase, cytochrome oxidase; (c) concentration of reduced glutathione (GSH). Before the first peroxidative stress induction, the rats are administered for 8 weeks by intraperitoneal injection of vehicle,

papaverine, delta-yohimbine, almitrine or hopanthenate. The rats are treated also during the week(s) before the second or third peroxidative stress. The cerebral peroxidative stress induces: (a) initially, a decrease in brain GSH concentration concomitant with a decrease in the mitochondrial activity of cytochrome oxidase of aa3-type (complex IV), without changes in ubiquinone and cytochrome b populations; (b) subsequently, an alteration in the transfer molecule cytochrome c and, finally, in rotenone-sensitive NADH-cytochrome c reductase (complex I) and succinate dehydrogenase (complex II). The selective sensitivity of the chain components to peroxidative stress is supported by the effects of the concomitant subchronic treatment with agents acting at different biochemical steps. In fact, almitrine sets limits to its effects at cytochrome c content and aa3-type cytochrome oxidase activity, while delta-yohimbine sets limits to its effects at the level of tricarboxylic acid cycle (citrate synthase) and/OT of intermediary between tricarboxylic acid cycle and complex II (succinate dehydrogenase). The effects induced by sequential peroxidative stress and drug treatment are supportive of the hypothesis that leakage of electrons (as a mandatory side-effect of the normal flux of electrons from both NADH and succinate to molecular oxygen) would be due to alteration in both availability of GSH and the content of components in the respiratory chain associated to energy-transducing system. In this field there is a cascade of derangements involving, at the beginning, the complex IV and, subsequently, other chain components, including cytochrome c and, finally, complexes II and I.

Berger A. 2000. Parkinson's disease linked with pesticide. Br Med J 321(7270): 1175.

Berger A. 2000 Nov 11. Parkinson's disease linked with pesticide. BMJ 321 (7270):1175A.

Betarbet R, Sherer TB, Greenamyre JT. 2002. Animal models of Parkinson's disease. Bioessays 24(4):308-318.
Abstract: Animal models are important tools in experimental medical science to better understand pathogenesis of human diseases. Once developed, these models can be exploited to test therapeutic approaches for treating functional disturbances observed in the disease of interest. On the basis of experimental and clinical findings, Parkinson's disease (PD) was the first neurological disease to be modeled and, subsequently, to be treated by neurotransmitter replacement therapy. Agents that selectively disrupt or destroy catecholaminergic systems, such as reserpine, methamphetamine, 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine have been used to develop PD models. Recently, it has been found that agricultural chemicals, such as rotenone and paraquat, when administered systemically, can reproduce specific features of PD in rodents, apparently via oxidative damage. Transgenic animals that over-express a-synuclein are used to study the role of this protein in dopaminergic degeneration. This review critically discusses animal models of PD and compares them with characteristics of the human disease. (C)

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Betarbet R, Sherer TB, Mackenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. 2000. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 3(12):1301-1306.
Abstract: The cause of Parkinson's disease (PD) is unknown, but epidemiological studies suggest an association with pesticides and other environmental toxins, and biochemical studies implicate a systemic defect in mitochondrial complex I. We report that chronic, systemic inhibition of complex I by the lipophilic pesticide, rotenone, causes highly selective nigrostriatal dopaminergic degeneration that is associated behaviorally with hypokinesia and rigidity. Nigral neurons in rotenone-treated rats accumulate fibrillar cytoplasmic inclusions that contain ubiquitin and alpha - synuclein. These results indicate that chronic exposure to a common pesticide can reproduce the anatomical, neurochemical, behavioral and neuropathological features of PD.

Bhatt MH, Elias MA, Mankodi AK. 1999. Acute and reversible parkinsonism due to organophosphate pesticide intoxication - Five cases. Neurology 52(7): 1467-1471.
Abstract: Objective: To describe five patients who developed acute and reversible parkinsonism following organophosphate (OP) pesticide exposure, and to consider whether this syndrome represents a rare sequela of such exposure in genetically susceptible individuals. Background: Several toxins are known to produce parkinsonism following acute exposure. Although case- control studies have implicated OP pesticides in the etiology of PD, acute parkinsonism following brief pesticide exposure has never been reported. Methods: The authors describe the clinical syndrome affecting five patients who presented with recent OP exposure and symptoms of an acute akinetic-rigid syndrome. Results: All patients developed parkinsonism that resembled PD clinically except for poor response to levodopa. Three genetically related patients were exposed to pesticides in a common environment before onset of parkinsonism; other family members remained unaffected. Other secondary causes of parkinsonism were excluded. Four patients recovered completely without treatment, and one patient was lost to follow-up. One patient experienced repeated episodes of parkinsonism with inadvertent reexposure to a pesticide-contaminated environment. Conclusion: The clinical course of these five patients suggests their syndrome represents a heretofore undescribed toxic effect of OP pesticides. Our observations strengthen epidemiologic studies implicating OP pesticides in the etiology of PD. a genetic susceptibility to OP pesticide-induced parkinsonism may account for three family members developing this syndrome.

Binda C, Hubalek F, Li M, Herzig Y, Sterling J, Edmondson DE, Mattevi A. 2005. Binding of rasagiline-related inhibitors to human monoamine oxidases. a kinetic and crystallographic analysis. J Med Chem 48(26):8148-8154.
Abstract: Monoamine oxidases A and B (MAO A and B) catalyze the degradation of neurotransmitters and represent drug targets for the treatment of neurodegenerative disorders. Rasagiline is an irreversible,

MAO B-selective inhibitor that has been approved as a novel anti-Parkinson's drug. In this study, we investigate the inhibition of recombinant human MAO A and MAO B by several rasagiline analogues. Different substituents added onto the rasagiline scaffold alter the binding affinity depending on the position on the aminoindan ring and on the size of the substituent. Compounds with a hydroxyl group on either the C4 or the C6 atom inhibit both isozymes, whereas a bulkier substituent such as a carbamate is tolerated only at the C4 position. The 1.7 angstrom crystal structure of MAO B in complex with 4-(N-methyl-N-ethyl-carbamoyloxy)-Nmethyl-N-propargyl-1(R)-aminoindan shows that the binding mode is similar to that of rasagiline with the carbamate moiety occupying the entrance cavity space. 1(R)-Aminoindan, the major metabolic product of rasagiline, and its analogues reversibly inhibit both XIAO A and MAO B. The crystal structure of N-methyl-1(R)-aminoindan bound to MAO B shows that its aminoindan ring adopts a different orientation compared to that of rasagiline.

Birchmachin MA, Briggs HL, Saborido AA, Bindoff LA, Turnbull DM. 1994. An evaluation of the measurement of the activities of complexes i-iv in the respiratory-chain of human skeletal-muscle mitochondria. Biochem Med Metab Biol 51(1):35-42.
Abstract: The measurement of individual respiratory chain complexes is an important component of the investigation of diseases due to mitochondrial dysfunction. We have evaluated assays which measure complexes I to IV in human skeletal muscle mitochondria and in addition optimized these assays to provide sensitive and reliable diagnostic techniques, particularly in situations where a partial interruption at a single complex needs to identified. Using several established methods of membrane disruption we have found that optimal activities of complexes I and II are obtained by freeze-thawing the mitochondria in hypotonic potassium phosphate buffer, whereas complex III and IV activities are markedly increased by the addition of the detergent n-dodecyl-beta-D-maltoside. Complex I activity is measured in the presence of 2.5 mg.ml(-1) bovine serum albumin, which increases rotenone sensitivity, and we have shown that NADH-cytochrome b(5) reductase makes an important contribution to the rotenone-insensitive NADH-ubiquinone oxidoreductase activity. Complex II activity is measured after preincubation of the mitochondrial fraction with succinate to fully activate the complex. Complex I and III activities are dependent upon the length of the isoprenoid chain of the ubiquinone and ubiquinol, respectively. These assays have been used to establish a control range. (C) 1994 Academic Press, Inc.

Blandini F, Greenamyre JT. 1995. Assay of [h-3] dihydrorotenone binding to complex-i in intact human platelets. Anal Biochem 230(1):16-19.
Abstract: We have developed an assay for the binding of [H-3] dihydrorotenone ([H-3]DHR), an analogue of the pesticide rotenone, to the mitochondrial enzyme, complex I, in intact human platelets. The highly hydrophobic nature of dihydrorotenone, which diffuses easily through biological membranes, rendered the isolation of mitochondrial fractions unnecessary. This allowed us to reduce the amount of blood required and

to shorten the processing of samples considerably. [H-3]DHR binding was saturable, specific, and highly reproducible. We also found that MPP(+) (1-methyl-4-phenylpyridinium species), which is accumulated actively by platelets, inhibited [H-3]DHR specific binding in a concentration-dependent manner. This method could provide a simple tool for the study of complex I in those disorders, such as Parkinson's disease (PD), in which a defect of this enzyme has been suggested. (C) 1995 Academic Press, Inc.

Blandini F, Nappi G, Greenamyre JT. 1998. Quantitative study of mitochondrial complex I in platelets of parkinsonian patients. Mov Disord 13(1):11-15.
Abstract: Activity of mitochondrial enzyme complex I (NADH-ubiquinone oxidoreductase) is reduced in the substantia nigra of patients with Parkinson's disease (PD). A less pronounced decrease in the activity of this enzyme has also been reported in platelets of PD patients. To obtain quantitative information on platelet complex I in PD, we studied platelet complex I in 16 PD patients and 16 age-matched controls by using a newly developed technique based on the binding of [H-3]dihydrorotenone ([H-3] DHR), an analog of the pesticide rotenone, to complex I. We also investigated the inhibitory effect of MPP+ (1-methyl-4-phenyl-pyridinium) on [H-3]DHR specific binding to platelet complex I. PD patients and controls showed similar levels of [H-3]DHR specific binding; preincubation of platelets with MPP+ caused the same degree of inhibition of [3H]DHR specific binding in the two groups. In PD patients, we observed a direct correlation between MPP+-induced inhibition of [H-3]DHR specific binding and the daily intake of levodopa, which may be related to drug-induced changes in the transport of MPP+ into the platelet or in its binding to complex I. These findings demonstrate that the reported reduction in complex I activity in platelets of PD patients can not be accounted for by an abnormality at the level of the rotenone binding site (putatively the ND-1 gene product), although they do not exclude differences in complex I activity between PD patients and controls.

Bleecker ML. 1988 Sep-Oct. Parkinsonism: a clinical marker of exposure to neurotoxins. Neurotoxicol Teratol 10(5):475-8.
Abstract: Parkinson must be viewed as a final common pathway resulting from a variety of neuropathological lesions which interfere with the integrity of the nigrostriatal system or its output. Exposure to a wide variety of neurotoxic compounds, namely, carbon monoxide, carbon disulfide, manganese and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), are associated with parkinsonism that has a varying neuropathology, which will be discussed.

Bloomquist JR. 2003. Low-dose effects of insecticides to dopaminergic pathways involved in Parkinsonism. Abstracts of Papers of the American Chemical Society 225:U95.

Bloomquist JR. 2004. Insecticide exposure in the MPTP-treated C57 mouse model of Parkinson's disease. Abstracts of Papers of the American Chemical Society 228:U88.

Bloomquist JR, Barlow RL, Gillette JS, Li W, Kirby ML. 2002. Selective effects of insecticides on nigrostriatal dopaminergic nerve pathways. Neurotoxicology 23(4-5):537-544.
Abstract: A degeneration of the nigrostriatal pathway is a primary component of Parkinson's disease (PD), and we have investigated the actions of insecticides on this pathway. For in vivo exposures, C57BL/6 mice were treated three times over a 2-week period with heptachlor the pyrethroids deltamethrin and permethrin, or chlorpyrifos. One day after the last treatment, we observed that heptachlor and the pyrethroids increased maximal [H-3]dopamine uptake in striatal synaptosomes from treated mice, with dose-dependent changes in V-max displaying a bell-shaped curve. Western blot analysis confirmed increased levels of dopamine transporter (DAT) protein in the striatum of mice treated with heptachlor and permethrin. In contrast, we observed a small, but statistically significant decrease in dopamine uptake by 100 mg/kg chlorpyrifos. For heptachlor doses that upregulated DAT expression had little or no effect on serotonin transport. Permethrin did cause an upregulation of serotonin transport, but required a 30-fold greater dose than that effective on dopamine uptake. Other evidence of specificity was found in transmitter release assays, where heptachlor and deltamethrin released dopamine from striatal terminals with greater potency than other transmitter types. These findings confirm that insecticides possess specificity for effects on striatal dopaminergic neurotransmission. (C) 2002 Elsevier Science Inc. All rights reserved.

Bocchetta A, Corsini GU. 1986. Parkinsons-disease and pesticides. Lancet 2 (8516):1163.

Bonetta L. 2002. Pesticide-Parkinson link explored. Nat Med 8(10):1050.

Bonneh-Barkay D, Langston WJ, Di Monte DA. 2005. Toxicity of redox cycling pesticides in primary mesencephalic cultures. Antioxidants & Redox Signaling 7(5-6):649-653.
Abstract: A loss of nigrostriatal dopaminergic neurons is the primary neurodegenerative feature of Parkinson's disease. Paraquat, a known redox cycling herbicide, has recently been shown to kill selectively nigrostriatal dopaminergic cells in the mouse model. The purpose of this study was to test the ability of paraquat and other redox cycling pesticides to damage dopaminergic neurons in primary mesencephalic cultures. Addition of paraquat, diquat, or benzyl viologen to mesencephalic cultures induced morphological changes (e.g., dystrophic neuronal processes) consistent with dopaminergic cell injury. The three pesticides also caused cell death as assessed by a reduction of the number of tyrosine hydroxylase-immunoreactive neurons and a dose-dependent decrease in [H-3]dopamine uptake. Quite interestingly, diquat and benzyl viologen were significantly more toxic than paraquat, probably reflecting their more pronounced ability to trigger redox cycling reactions. The data support a role of redox cycling as a mechanism of dopaminergic cell degeneration and suggest that the property of redox cycling should be taken into consideration when evaluating putative environmental risk factors for

Parkinson's disease.

Bonneh-Barkay D, Reaney SH, Langston WJ, Di Monte DA. 2005. Redox cycling of the herbicide paraquat in microglial cultures. Molecular Brain Research 134 (1):52-56.
Abstract: Mechanisms involved in paraquat neurotoxicity that selectively target nigrostriatal dopaminergic neurons remain relatively unknown. In this study, we tested the hypotheses that paraquat exposure leads to the production of reactive oxygen species (ROS) through a process of redox cycling and that microglia represent an important site for the initiation of redox cycling reactions. Addition of paraquat to N9 microglial cultures resulted in a dose- and time-dependent release of superoxide radicals. Other agents that share with paraquat the property of redox cycling, i.e., benzyl viologen and diquat, also induced a marked production of superoxide radicals by microglia. The ability of paraquat, benzyl viologen, and diquat to induce superoxide release was correlated to their one-electron reduction potentials and thus their tendency to redox cycle. Nitric oxide synthase and NADPH oxidase were identified as enzymatic sources of electrons that triggered paraquat redox cycling by microglia. Taken together, these data provide evidence in favor of a new mechanism by which microglia could play a role in oxidative injury during neurodegenerative processes. Microglial NOS and NADPH oxidase could promote the generation of ROS via the redox cycling of paraquat-like toxicants. (C) 2004 Elsevier B.V. All rights reserved.

Borm PJ, Van Vliet C. 1988 Nov. Susceptibility in Parkinson's disease. 'Of mice and men'. Med Hypotheses 27(3):205-7.
Abstract: Nowadays, a substantial amount of clinical and experimental research is directed to the role of reactive oxygen species in the pathogenesis of Parkinson's disease. On the other hand epidemiologic studies elicited the role of cytochrome P-450 and exposure to MPTP-analogues (such as paraquat) in the prevalence of this disease. Until now the relation between these two findings was not clear. In this paper a hypothesis is presented linking the present data on susceptibility towards Parkinson's disease.

Bougria M, Vitorica J, Cano J, Machado A. 1995. Implication of dopamine transporter system on 1-methyl-4-phenylpyridinium and rotenone effect in striatal synaptosomes. European Journal of Pharmacology-Molecular Pharmacology Section 291(3):407-415.
Abstract: The neurotoxic effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) seems to be produced by the inhibition of the respiratory chain by its metabolite 1-methyl-4-phenylpyridinium ion (MPP (+)). At the same time, its specific selectivity seems to be related especially to the dopamine uptake system. However, it is possible that other specific differences in dopaminergic neurons at the nigrostriatal system, such as constitutive metabolic deficiencies or other differences related to the energy capacity, could determine the greater vulnerability to MPP(+). We have addressed this point by studying the effect of MPP(+) and different inhibitors of the respiratory chain (rotenone, antimycin A and

KCN) on the maximal respiratory rate from both synaptosomes and isolated synaptosomal mitochondria from different brain areas, i.e. cortex, hippocampus and striatum, and in isolated liver mitochondria. The results demonstrate the absence of differences in the effect of the inhibitors in isolated mitochondria. In contrast, a greater inhibition was found in striatal synaptosomes than in cortical or hippocampal synaptosomes when MPP(+) and rotenone were used. Moreover, nomifensine or 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3 -phenylpropyl) piperazine dihydrochloride (GBR-12909), inhibitor of the dopamine uptake system, has a protective effect in both cases. Our study indicates the great importance of the dopamine uptake system in the vulnerability of the dopamine striatum system. Moreover, our results show the low selectivity of this dopamine uptake system that is able to transport actively compounds with different chemical structures such as dopamine, MPP(+) and rotenone.

Bourne JA. 2001. SCH 23390: The first selective dopamine D-1-like receptor antagonist. Cns Drug Reviews 7(4):399-414.
Abstract: SCH 23390, the halobenzazepine (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-IH-3-ben zazepine, is a highly potent and selective dopamine D-1-like receptor antagonist with a K-i of 0.2 and 0.3 nM for the D-1 and D-5 dopamine receptor sub-types, respectively. In vitro, it also binds with high affinity to the 5-HT2 and 5-HTIC serotonin receptor subtypes. However, the doses required to induce a similar response in vivo are greater than 10-fold higher than those required to induce a D-1-mediated response. Previous in vivo pharmacological studies with SCH 23390 have shown it to abolish generalized seizures evoked by the chemoconvulsants: pilocarpine and soman. These studies provide evidence of the potential importance of D-1-like dopaminergic receptor mechanisms in facilitating the initiation and spread of seizures. The inference from a majority of studies is that the activation of dopamine D, receptors facilitates seizure activity, whereas activation of D-2 receptors may inhibit the development of seizures. SCH 23390 has also been used in studies of other neurological disorders in which the dopamine system has been implicated, such as psychosis and Parkinson's disease. Apart from the study of neurological disorders, SCH 23390 has been extensively used as a tool in the topographical determination of brain D, receptors in rodents, nonhuman primates, and humans. In summary, SCH 23390 has been a major tool in gaining a better understanding of the role of the dopamine system, more specifically the D-1 receptor, in neurological function and dysfunction.

Bove J, Prou D, Perier C, Przedborski S. 2005 Jul. Toxin-induced models of Parkinson's disease. NeuroRx 2(3):484-94.
Abstract: Parkinson's disease (PD) is a common neurodegenerative disease that appears essentially as a sporadic condition. It results mainly from the death of dopaminergic neurons in the substantia nigra. PD etiology remains mysterious, whereas its pathogenesis begins to be understood as a multifactorial cascade of deleterious factors. Most insights into PD pathogenesis come from investigations performed in experimental

models of PD, especially those produced by neurotoxins. Although a host of natural and synthetic molecules do exert deleterious effects on dopaminergic neurons, only a handful are used in living laboratory animals to recapitulate some of the hallmarks of PD. In this review, we discuss what we believe are the four most popular parkinsonian neurotoxins, namely 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat. The main goal is to provide an updated summary of the main characteristics of each of these four neurotoxins. However, we also try to provide the reader with an idea about the various strengths and the weaknesses of these neurotoxic models.

Boyce N. 2000. Slow poisons - Gould pesticides be the cause of Parkinson's? New Scientist 168(2264):16.

Brennan M. 2000. Parkinson's pesticide connection reinforced. Chemical & Engineering News 78(46):10-11.

Bretaud S, Lee S, Guo S. 2004. Sensitivity of zebrafish to environmental toxins implicated in Parkinson's disease. Neurotoxicol Teratol 26(6):857-864.
Abstract: Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra and movement defects, including bradykinesia, tremor, and postural imbalance. Whereas the etiology and pathogenesis of PD is still poorly understood, studies in animal models are providing important insights. One valuable type of animal model for PD is established by treating animals with PD-inducing neurotoxins, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat. These neurotoxins are thought to inhibit mitochondrial complex I activity leading to oxidative stress, impaired energy metabolism, proteasomal dysfunction, and, eventually, dopamine neuronal loss. However, the genes and pathways that underlie the neurotoxicity of these agents are not known. In this study, we explored the effect of MPTP, rotenone, and paraquat in both adult and larval zebrafish, which are highly amenable to genetic analysis that can lead to the identification of the underlying genes and pathways. Here, we report that adult zebrafish display behavioral alterations, including decreased locomotor activity in response to MPTP, whereas larval zebrafish exhibited developmental, behavioral, and DA sensitivity to these agents. Taken together, these findings suggest that zebrafish could be a valuable model for genetically dissecting the molecular mechanisms underlying the neurotoxicity of PD-inducing agents. (C) 2004 Elsevier Inc. All rights reserved.

Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ. 1999. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res 823(1-2):1-10.
Abstract: The herbicide paraquat, bearing structural similarity to the known dopaminergic neurotoxicant MPTP, has been suggested as a potential etiologic factor in Parkinson's disease. Consideration of paraquat as a candidate neurotoxicant requires demonstration that systemic delivery

produces substantia nigra dopaminergic neuron loss and the attendant neurobehavioral syndrome reflecting depletion of dopamine terminals within the striatum. To address these issues paraquat was administered systemically into adult C57 b1/6 mice, ambulatory behavior monitored, substantia nigra dopamine neuron number and striatal dopamine terminal density quantified. The data indicate that paraquat like MPTP elicits a dose-dependent decrease in substantia nigra dopaminergic neurons assessed by a Fluoro-gold prelabeling method, a decline in striatal dopamine nerve terminal density assessed by measurement of tyrosine hydroxylase immunoreactivity; and neurobehavioral syndrome characterized by reduced ambulatory activity. Taken together, these data suggest that systemically absorbed paraquat crosses the blood-brain barrier to cause destruction of dopamine neurons in the substantia nigra, consequent reduction of dopaminergic innervation of the striatum and a neurobehavioral syndrome similar to the well characterized and bona fide dopaminergic toxin MPTP. (C) 1999 Elsevier Science B.V. All rights reserved.

Brophy VH, Jarvik GP, Richter RJ, Rozek LS, Schellenberg GD, Furlong CE. 2000. Analysis of paraoxonase (PON1) L55M status requires both genotype and phenotype. Pharmacogenetics 10(5):453-460.
Abstract: Paraoxonase (PON1) is tightly associated with high-density lipoprotein particles and is believed to contribute to the prevention of atherosclerosis by metabolizing oxidized lipids. PON1 also hydrolyses the bioactive oxon forms of organophosphorus pesticides such as parathion, diazinon and chlorpyrifos. Two common polymorphisms have been identified in the coding sequence of human PON1: L55M and R192Q. Several previous studies have found that the presence of the PON1(R192) allele raises the risk of cardiovascular disease while others found no correlation. The studies, however, have focused on the genotype of PON1 and not the expression level of the protein. We found that the PON1 expression level in plasma, as determined by the rates of paraoxon and diazoxon hydrolysis, varies widely among individuals and within a genotype. Previous studies found that individuals having Met at PON1(55) have lower levels of both PON1 mRNA and activity. In this study, we determined the plasma activity levels of PON1 and examined the relationships between PON1(55) genotype and PON1 level. As with PON1 (192), we found considerable overlap in activity among the PON155 genotypes. Of the 317 individuals whose PON1 status was determined in this study, 48.9% were PON1(Q192) homozygotes. Analysis of the PON1 (QQ192) population showed that while the average PON1 activity (diazoxon hydrolysis) was 12266 U/L for PON1(LL55) and 7777 U/L for PON1(MM55), a given PON1(MM55) individual could have more than twice the activity of a PON1(LL55) individual. PON1 status, which includes PON1 level as well as PON1(192) genotype, may be a better predictor for cardiovascular disease or organophosphate susceptibility than PON1 genotype alone. Pharmacogenetics 10:453-460 (C) 2000 Lippincott Williams & Wilkins.

Broussolle E, Thobois S. 2002. Genetic and environmental factors of Parkinson's disease. Rev Neurol (Paris) 158(Sp. Iss. 1):S11-S23.

Abstract: We present a review on the genetic and environmental factors implicated in the aetiology of Parkinson's disease. The environmental hypothesis was strongly suggested about 20 years ago after the report of a parkinsonian syndrome in young adults that were intoxicated by a neurotoxin called MPTP which selectively destroys nigrostriatal dopaminergic neurons. Several chemical products used in herbicides and pesticides are similar structurally to MPTP including paraquat, diquat and rotenone. Epidemiological studies have revealed an increased risk for Parkinson's disease with the use of pesticides and herbicides or the consumption of well water in rural areas of industrialised countries. However it has not been possible to identify any causative environmental chemical agent in the aetiology of Parkinson's disease despite intensive research. Comparatively, the genetic hypothesis of Parkinson's disease has gained considerable interest during the last decade. Epidemiological studies reveal a family history in 10-25 p. 100 Parkinson's disease patients. Several large kindreds with autosomal dominant Parkinson's disease associated with mutations of alpha-synuclein gene (PARK 1) were recently described. alpha-synuclein is a constituant of Lewy bodies, the hallmark of idiopathic Parkinson's disease. However (alpha-synuclein gene mutations are rare as opposed to parkin gene mutations (PARK 2), which are frequently found in autosomal recessive and sporadic young onset Parkinson's disease patients. Other genes or locus are implicated in autosomal dominant familial cases (PARK 3, 4 and 5). Nevertheless, a pure genetic origin can be demonstrated only in a minority of Parkinson's disease patients. Investigation of the possible interaction between genes and environment and of several candidate genes gave contradictory results, notably concerning the association between allelic variants of CYP2D6 gene and the occurrence of Parkinson's disease. In conclusion, the aetiology of Parkinson's disease remains unknown. There are probably several types or causes of Parkinson's disease. In most cases, this heterogeneity could be attributed both to genetic and environmental factors.

Brownson DM, Mabry TJ, Leslie SW. 2002. The cycad neurotoxic amino acid, beta-N-methylamino-L-alanine (BMAA), elevates intracellular calcium levels in dissociated rat brain cells. J Ethnopharmacol 82(2-3):159-167.
Abstract: Seeds of the Guam cycad Cycas micronesica K.D. Hill (Cycadaceae), which contain beta-methylamino-L-alanine (BMAA), have been implicated in the etiology of the devastating neurodisease ALS-PDC that is found among the native Chamorros on Guam. The disease also occurs in the native populations on Irian Jaya and the Kii Peninsula of Japan, and in all three areas the cycad seeds are used either dietarily or medically. ALS-PDC is a complex of amyotrophic lateral sclerosis and parkinsonism dementia complex with additional symptoms of Alzheimer's. It is well known that Ca2+ elevations in brain cells can lead to cell death and neurodiseases. Therefore, we evaluated the ability of the cycad toxin BMAA to elevate the intracellular calcium concentration ([Ca2+](i)) in dissociated newborn rat brain cells loaded with fura-2 dye. BMAA produced an increase in intracellular calcium levels in a concentration-dependent

manner. The increases were dependent not only on extracellular calcium concentrations, but also significantly on the presence of bicarbonate ion. Increasing concentrations of sodium bicarbonate resulted in a potentiation of the BMAA-induced [Ca2+](i) elevation. The bicarbonate dependence did not result from the increased sodium concentration or alkalinization of the buffer. Our results support the hypothesis that the neurotoxicity of BMAA is due to an excitotoxic mechanism, involving elevated intracellular calcium levels and bicarbonate. Furthermore, since BMAA alone produced no increase in Ca2+ levels, these results suggest the involvement of a product of BMAA and CO2, namely a beta-carbamate, which has a structure similar to other excitatory amino acids (EAA) such as glutamate; thus, the causative agent for ALS-PDC on Guam and elsewhere may be the beta-carbamate of BMAA. These findings support the theory that some forms of other neurodiseases may also involve environmental toxins. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Bursch W, Ellinger A. 2005. Autophagy - a basic mechanism and a potential role for neurodegeneration. Folia Neuropathol 43(4):297-310.
Abstract: Autophagy constitutes a fundamental survival strategy of cells; its disturbance contributes to the pathogenesis of cancer, liver and immune disease, pathogen infection, myopathies as well as neurodegenerative disorders such as Amyotrophic lateral sclerosis, Parkinson;s, Huntington;s and Alzheimer;s disease. The pathogenesis of neurodegenerative diseases also involves a gradual and progressive loss of neuronal cells. Cells may use different pathways for active self-destruction as reflected by different morphology: while in apoptosis (or "type I") nuclear fragmentation associated with cytoplasmic condensation but preservation of organelles is predominant, autophagic degradation of the cytoplasmic structures preceding nuclear collapse is a characteristic of a second type of programmed cell death (PCD). Linking autophagy to programmed cell death initiated a controversial discussion on how a suggested role of autophagy in cell suicide might meet with its established survival function. To some extent, the diverse morphologies can be associated with distinct biochemical and molecular events [caspase-dependent and -independent death programs, DAP-kinase activity, Ras-expression, induction of autophagy genes, fate of cytoskeleton, among others]. However, there is a broad overlap between cell death pathways. Conceivably, diverse PCD programs emerged during evolution, the conservation of which allows eukaryotic cells a flexible response to physiological or pathological demands.

Butcher J. 2000. Scientists suggest a link between rotenone and Parkinson's disease. Lancet 356(9242):1659.

Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, Nutt JG. 1993. Environmental antecedents of young-onset parkinsons-disease. Neurology 43(6):1150-1158.
Abstract: We conducted an exploratory study of young-onset Parkinson's disease (YOPD) to examine occupational and environmental factors associated with disease risk. This case-control study included 63 YOPD

patients (diagnosis on or before age 50); controls (n = 68) were diagnosed with rheumatoid arthritis. Crude odds ratios (ORs) were computed to identify exposure variables for logistic regression analyses. After controlling for the variables of race, educational level, sex, age, age at diagnosis, and family history of Parkinson's disease (PD), PD was positively associated with insecticide exposure (OR = 5.75, p < 0.001), past residency in a fumigated house (OR = 5.25, p = 0.046), herbicide exposure (OR = 3.22, p = 0.033), rural residency at time of diagnosis (OR = 2.72, p = 0.027), and nuts and seed eating 10 years before diagnosis (OR = 1.49, p = 0. 02 1). PD was inversely associated with cigarette smoking at 5 years (OR = 0.50, p = 0.027), 10 years (OR = 0.43, p = 0.012), and 15 years (OR = 0.37, p = 0.005) before diagnosis, farm residency (OR = 0.38, p = 0.018), and exposure to dimethyl sulfoxide (OR = 0.10, p < 0.001). These findings are consistent with hypotheses linking PD to exposure to pesticide agents.

Bywood PT, Johnson SM. 2003. Mitochondrial complex inhibitors preferentially damage substantia nigra dopamine neurons in rat brain slices. Exp Neurol 179(1):47-59.
Abstract: Using a rat brain slice preparation, we investigated the role of energy impairment on the selective loss of dopamine neurons in the substantia nigra (SN). Brain slices (400 pm) were incubated at 35degreesC for 2 h in the presence or absence of mitochondrial complex inhibitors, rotenone, MPP+, 3-nitropropionic acid, and antimycin A. Slices were also incubated in rotenone with excitatory amino acid (EAA) receptor antagonists, MK-801 and CNQX, to determine whether rotenone-induced damage was mediated by EAAs. The slices were then fixed, recut into 30-mum sections, and immunolabeled for tyrosine hydroxylase (TH) to identify catecholamine neurons and to quantify loss of TH-labeled dendrites after treatment. Quantitative comparison was made between SN dopamine neurons, in which rotenone-induced dendrite loss was severe, and hypothalamic All dopamine neurons, which were spared. Adjacent sections that were immunolabeled for calbindin or stained with cresyl violet also revealed a striking dendritic degeneration of SN neurons in rotenone-exposed slices, whereas noncatecholamine neurons, such as those in the perifornical nucleus (PeF), were more resistant. Preferential damage to SN dopamine neurons was also evident with other mitochondrial complex inhibitors, MPP+ and antimycin A. EAA receptor antagonists provided partial protection to SN neurons in slices incubated with rotenone (3 muM). The particular vulnerability of SN dopamine neurons in the slice is consistent with the vulnerability of SN in Parkinson's disease. The selective effect of mitochondrial complex inhibition in SN dopamine neurons implies a fundamental deficit in the capacity of these neurons to defend against toxic insult. (C) 2002 Elsevier Science (USA).

Caban-Holt A, Mattingly M, Cooper G, Schmitt FA. 2005. Neurodegenerative memory disorders: A potential role of environmental toxins. Neurol Clin 23 (2):485-+.
Abstract: This article summarizes research literature that evaluates putative environmental exposure to toxins and their potential association

with neurodegenerative disorders. Included are the environmental toxins such as solvents, metals, pesticides, magnetic field exposure, and smoking. Because most information about toxins and neurodegeneration is derived from laboratory models and epidemiologic research, causality is difficult to infer when these data are generalized to populations or applied to individual patients.

Caboni P, Sherer TB, Zhang NJ, Taylor G, Na HM, Greenamyre JT, Casida JE. 2004. Rotenone, deguelin, their metabolites, and the rat model of Parkinson's disease. Chem Res Toxicol 17(11):1540-1548.
Abstract: Rotenone and deguelin are the major active ingredients and principal components of cube resin from Lonchocarpus utilis used as a botanical insecticide and piscicide. They are also potent complex I (NADH:ubiquinone oxidoreductase) inhibitors. Rotenone was known earlier, and deguelin is shown here to induce a Parkinson's disease (PD)-like syndrome after subcutaneous treatment of rats by osmotic minipump. Rotenone at 3 mg/kg/day or deguelin at 6 but not 3 mg/kg/day induces degeneration of the nigrostriatal dopaminergic pathway, as shown by reduced tyrosine hydroxylase immunoreactivity with treatments for 5 or 6 days. The neuropathological. lesions are associated with a brain level of parent rotenoid of 0.4-1.3 ppm but not with the much smaller brain level of 12abeta-hydroxyrotenoids or other metabolites analyzed by HPLC and LC/MS. We previously established that the hydroxylated metabolites and derivatives of rotenone and deguelin are all less active (i.e., detoxified) as complex I inhibitors relative to the parent rotenoids. The PD-like syndrome induced in rats by rotenone and deguelin is therefore due to the parent compounds rather than metabolites. Deguelin is about half as active as rotenone in inducing the PD-like syndrome in rats and in acute ip LD50 in mice. Rotenone and deguelin are metabolized by human recombinant 3A4 and 2C19 but not five other P450 enzymes. 2C19 is more selective than 3A4 in forming the 12abeta-hydroxyrotenoids. Identified sites of metabolic attack individually or in combination are as follows: 12abeta hydroxylation and 2-O-demethylation of both compounds, oxidation of the rotenone isopropenyl substituent to mono and diol derivatives, and probable oxidation of the deguelin dimethylehromene double bond. These toxicological features must be considered in using rotenone, deguelin, and their analogues as pesticides, candidate radioimaging and cancer chemopreventive agents, and models of PD.

Cammack R, Shergill JK, Inalsingh VA, Hughes MN. 1998. Applications of electron paramagnetic resonance spectroscopy to study interactions of iron proteins in cells with nitric oxide. Spectrochim Acta A Mol Biomol Spectrosc 54(14): 2393-2402.
Abstract: Nitric oxide and species derived from it have a wide range of biological functions. Some applications of electron paramagnetic resonance (EPR) spectroscopy are reviewed, for observing nitrosyl species in biological systems. Nitrite has long been used as a food preservative owing to its bacteriostatic effect on spoilage bacteria. Nitrosyl complexes such as sodium nitroprusside, which are added experimentally as NO-generators, themselves produce paramagnetic nitrosyl species, which may be seen by

EPR. We have used this to observe the effects of nitroprusside on clostridial cells. After growth in the presence of sublethal concentrations of nitroprusside, the cells show they have been converted into other, presumably less toxic, nitrosyl complexes such as (RS)(2)Fe(NO)(2). Nitric oxide is cytotoxic, partly due to its effects on mitochondria. This is exploited in the destruction of cancer cells by the immune system. The targets include iron-sulfur proteins. It appears that species derived from nitric oxide such as peroxynitrite may be responsible. Addition of peroxynitrite to mitochondria led to depletion of the EPR-detectable iron-sulfur clusters. Paramagnetic complexes are formed in vivo from hemoglobin, in conditions such as experimental endotoxic shock. This has been used to follow the course of production of NO by macrophages. We have examined the effects of suppression of NO synthase using biopterin antagonists. Another method is to use an injected NO-trapping agent, Fe-diethyldithiocarbamate (Fe-DETC) to detect accumulated NO by EPR. In this way we have observed the effects of depletion of serum arginine by arginase. In brains from victims of Parkinson's disease, a nitrosyl species, identified as nitrosyl hemoglobin, has been observed in substantia nigra. This is an indication for the involvement of nitric oxide or a derived species in the damage to this organ. (C) 1998 Elsevier Science B.V. All rights reserved.

Carmine A, Buervenich S, Sydow O, Anvret M, Olson L. 2002. Further evidence for an association of the paraoxonase 1 (PON1) Met-54 allele with Parkinson's disease. Mov Disord 17(4):764-766.
Abstract: Paraoxonase1 (PON1) is an arylesterase mainly expressed in the liver that hydrolyzes organophosphates such as pesticides, reported risk factors for Parkinson's disease (PD), and other neurotoxins. A Leu-Met 54 polymorphism in the,gene for PON1-affecting : enzyme activity was recently shown, employing a new restriction enzyme technique, to be associated with Parkinson's disease. We examined the same polymorphism by automated capillary sequencing in a sample of Caucasian subjects from the Stockholm area in Sweden (127 healthy individuals and 114 patients with PD) and found similar distributions and a similar difference in our sample. The Genotype distribution in our PD material was LL 36.0%, LM 45.6%, and MM 18.4%; in our control material, it was LL 45.7%, LM 44.1%, and MM 10.2%. Based on the previously established increase in allele frequencies of the lower-activity Met-variant of PON1, we could confirm a significant association using a one-sided chi(2) test. Results remained significant with a two-sided chi(2) test, allowing for both increases and decreases in frequencies. Our data confirm an association between the PON1 Leu-Met 54 polymorphism and PD by demonstrating a similar association. The distribution between familial and non-familial PD patients was equal. No other synonymous or non-synonymous polymorphisms were found in the sequenced coding region of PON1. (C) 2002 Movement Disorder Society.

Carmody RJ, Mcgowan AJ, Cotter TG. 1999. Reactive oxygen species as mediators of photoreceptor apoptosis in vitro. Exp Cell Res 248(2): 520-530.

Abstract: Retinitis pigmentosa is a heterogeneous group of retinal degenerations characterized by a progressive loss of photoreceptors through the process of apoptosis. The apoptotic cell death of photoreceptors appears to represent a final common pathway in the pathology of retinitis pigmentosa. Previous studies have reported the ability of antioxidants to ameliorate light-induced retinal degeneration, suggesting a role for oxidative stress in photoreceptor cell death. This study demonstrates an early and sustained increase in intracellular reactive oxygen species accompanied by a rapid depletion of intracellular glutathione in an in vitro model of photoreceptor apoptosis. These early changes in the cellular redox state precede disruption of mitochondrial transmembrane potential, nuclear condensation, DNA nicking, and cell shrinkage, all of which are well-characterized events of apoptotic cell death. The ability of zinc chloride and pyrrolidine dithiocarbamate, two established antioxidants, to inhibit photoreceptor apoptosis through the scavenging of intracellular reactive oxygen species establishes a role for reactive oxygen species as possible mediators of in vitro photoreceptor apoptosis. This study provides a molecular basis for the inhibition of photoreceptor apoptosis by antioxidants. (C) 1999 Academic Press.

Carreiras MC, Marco JL. 2004. Recent approaches to novel anti-Alzheimer therapy. Curr Pharm Des 10(25):3167-3175.
Abstract: Insufficient cholinergic neurotransmission in AD is responsible for a progressive loss of cognition and motor capacities. The cholinergic hypothesis has provided the rationale for the current treatment approaches based on acetylcholinesterase inhibitors. However, recent data focus on the complex nature of AD and disclose the involvement of other neurotransmitters such as serotonin, noradrenalin, dopamine, histamine, excitatory amino acids and neuropeptides among others. Interestingly, recent research has revealed that in severe AD brains the levels of AChE are considerably reduced whereas BuChE activity increases, thus aggravating the toxicity of betaA. In such instances, it is possible that BuChE may be a more suitable target than AChE. Oxidative stress has been implicated in CNS degenerative disorders such as AD and PD. Therefore, owing to their capacity to inhibit oxidative damage, MAOIs are potential candidates as anti-Alzheimer drugs. More recently, a novel drug - TV3326 - was designed, based upon two pharmacophores: the carbamate moiety from rivastigmine, an AChE inhibitor; and the propargyl group from rasagiline, a MAO inhibitor. This drug exhibits cholinesterase and selective brain MAO inhibitory activities, reduces apoptosis and stimulates the processing of APPalpha, hence reducing the possibility of generation of the toxic betaA. Thus, TV3326 may be expected to contribute positively to the cognitive benefits of Alzheimer's patients. Anyhow, the development of drugs with several targets and diverse pharmacological properties may conclusively demonstrate the most beneficial therapy.

Casey DE. 1998. Effects of clozapine therapy in schizophrenic individuals at risk for tardive dyskinesia. J Clin Psychiatry 59 Suppl 3:31-7.
Abstract: Neuroleptics were the first modern class of pharmacotherapeutic agents available for the treatment of schizophrenia. Although they were

effective in reducing florid psychotic symptoms, up to 90% of treated individuals subsequently developed extrapyramidal symptoms (EPS) (akathisia, dystonia, or parkinsonism), and about 20% developed tardive dyskinesia (TD). When clozapine became commercially available for treatment-resistant and treatment-intolerant (i.e., prone to EPS and TD) schizophrenic individuals, it became apparent that an antipsychotic need not induce motor side effects to be efficacious in reducing the symptomatology of schizophrenia. Sociodemographic, behavioral, and clinical predictors of TD are useful in identifying a subset of schizophrenic individuals who would benefit from treatment with clozapine, the prototype atypical antipsychotic whose efficacy and motor side effect profile are superior to those of chlorpromazine. This favorable motor side effect profile of clozapine contributes to improved patient outcomes by reducing noncompliance, substance abuse, and suicide, resulting in improved quality of life and savings on health care costs.

Cassarino DS, Parks JK, Parker WD, Bennett JP. 1999. The parkinsonian neurotoxin MPP+ opens the mitochondrial permeability transition pore and releases cytochrome c in isolated mitochondria via an oxidative mechanism. Biochimica Et Biophysica Acta-Molecular Basis of Disease 1453 (1):49-62.
Abstract: The mitochondrial transition pore (MTP) is implicated as a mediator of cell injury and death in many situations. The MTP opens in response to stimuli including reactive oxygen species and inhibition of the electron transport chain. Sporadic Parkinson's disease (PD) is characterized by oxidative stress and specifically involves a defect in complex I of the electron transport chain. To explore the possible involvement of the MTP in PD models, we tested the effects of the complex I inhibitor and apoptosis-inducing toxin N-methyl-4-phenylpyridinium (MPP +) on cyclosporin A (CsA)-sensitive mitochondrial swelling and release of cytochrome c. In the presence of Ca2+ and P-i, MPP+ induced a permeability transition in both liver and brain mitochondria. MPP+ also caused release of cytochrome c from liver mitochondria. Rotenone, a classic non-competitive complex I inhibitor, completely inhibited MPP+-induced swelling and release of cytochrome c. The MPP+-induced permeability transition was synergistic with nitric oxide and the adenine nucleotide translocator inhibitor atractyloside, and additive with phenyl arsine oxide cross-linking of dithiol residues. MPP+-induced pore opening and cytochrome c release were blocked by CsA, the Ca2+ uniporter inhibitor ruthenium red, the hydrophobic disulfide reagent N-ethylmaleimide, butacaine, and the free radical scavenging enzymes catalase and superoxide dismutase. MPP+ neurotoxicity may derive from not only its inhibition of complex I and consequent ATP depletion, but also from its ability to open the MTP and to release mitochondrial factors including Ca2+ and cytochrome c known to be involved in apoptosis. (C) 1999 Elsevier Science B.V. All rights reserved.

Caudle WM, Richardson JR, Wang MZ, Miller GW . 2005. Perinatal heptachlor exposure increases expression of presynaptic dopaminergic markers in mouse striatum. Neurotoxicology 26(4):721-728.

Abstract: Although banned in the 1970s, significant levels of the organochlorine pesticide heptachlor are still present in the environment raising concern over potential human exposure. In particular, organochlorine pesticides have been linked to an increased risk of Parkinson's disease. Studies from our laboratory and others have demonstrated that exposure of laboratory animals to heptachlor alters the levels and function of the dopamine transporter (DAT), an integral component of dopaminergic neurotransmission and a gateway for the dopaminergic neurotoxin MPTR In this study, we examined the effects of developmental exposure to heptachlor on DAT and other key components of the dopaminergic system, including the vesicular monoamine transporter 2 (VMAT2), tyrosine hydroxylase (TH), and aromatic amino acid decarboxylase (AADC). Female C57BL/6J mice received 0 or 3 mg/kg heptachlor in peanut butter every 3 days for 2 weeks prior to breeding and throughout gestation and lactation until the offspring were weaned on postnatal day (PND) 21. On postnatal day 28, DAT VMAT2, and TH levels were increased by 100, 70, and 30%, respectively, with no change in AADC levels or total dopamine levels. The ratio of DAT:VMAT2 was increased 29%. Since an increase in the DAT:VMAT2 ratio appears to predict susceptibility of brain regions to Parkinson's disease (PD) and results in increased toxicity of MPTP these results suggest that alterations of the dopaminergic system by developmental heptachlor exposure may increase the susceptibility of dopamine neurons to toxic insult. (c) 2004 Elsevier Inc. All rights reserved.

Caughlan A, Newhouse K, Namgung U, Xia ZG. 2004. Chlorpyrifos induces apoptosis in rat cortical neurons that is regulated by a balance between p38 and ERK/JNK MAP kinases. Toxicol Sci 78(1):125-134.
Abstract: Chlorpyrifos, an acetylcholinesterase (AChE) inhibitor, is a widely used organophosphate pesticide. Recent concern has focused on its neurotoxicity that is not attributable to AChE inhibition. Here, we report that chlorpyrifos and chlorpyrifos-oxon, but not 3,5,6-trichloro-2-pyridinol (TCP; the breakdown product of chlorpyrifos and chlorpyrifos-oxon), induce apoptosis in primary cortical neurons cultured from embryonic day 17 or newborn rats. It is generally agreed that chlorpyrifos-oxon is approximately three orders of magnitude more potent than chlorpyrifos in inhibition of brain acetylcholinesterase activity. However, our data demonstrate that chlorpyrifos-oxon is only slightly more potent than chlorpyrifos in inducing apoptosis. This indicates that chlorpyrifos-induced apoptosis may occur independently of AChE inhibition, although AChE activity was not measured in this study. Furthermore, chlorpyrifos activates the ERK1/2 and p38 MAP kinases. Surprisingly, blocking ERK1/2 activation by the MEK inhibitor SL327 caused a small but statistically significant inhibition of apoptosis, while blocking p38 with SB202190 significantly accelerated apoptosis induced by chlorpyrifos. This suggests a pro- and anti-apoptotic role for ERK1/2 and p38, respectively. Although chlorpyrifos did not stimulate total JNK activity, it caused a sustained activation of a sub-pool of JNK in the nucleus and stimulated phosphorylation of c-Jun, a downstream target of JNK. Transient expression of a dominant negative c-

Jun mutant inhibited chlorpyrifos-induced apoptosis, suggesting a role for JNK and JNK-mediated transcription in this cell death. Together, our data suggest apoptosis as a novel toxic endpoint of chlorpyrifos neurotoxicity in the brain that may be independent of AChE inhibition. Furthermore, activation of the ERK1/2 and JNK MAP kinases contributes to, while activation of the p38 MAP kinase counteracts chlorpyrifos-induced apoptosis in cortical neurons.

Chan DKY, Woo J, Ho SC, Pang CP, Law LK, Ng PW, Hung WT, Kwok T, Hui E, Orr K, Leung MF, Kay R. 1998. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry 65(5):781-784.
Abstract: An epidemiological study of the environmental and genetic factors as well as the possible interplay between them was conducted among 215 patients with Parkinson's disease and 313 controls in a Chinese population in Hong Kong. In univariate analysis, a regular tea drinking habit was found to be a protective factor, which had not been reported before. Smoking (a protective factor), family history, duration of pesticide exposure (in years) in farming and pesticide exposure during farming in women (both risk factors) have been reported previously. In multivariate analysis, current smoking reached borderline significance at the 5% level and the variables, years exposed to pesticides and family history were significant at the 10% level. By contrast with the common occurrence of polymorphism of the CYP2D6 gene (a gene involved with xenobiotic metabolism) in white people, it is very rare in China and is not thought to be a significant factor contributing to Parkinson's disease in Chinese people.

Chan TS, Teng S, Wilson JX, Galati G, Khan S, O'brien PJ. 2002. Coenzyme Q cytoprotective mechanisms for mitochondrial complex I cytopathies involves NAD(P)H: Quinone oxidoreductase 1(NQO1). Free Radic Res 36 (4):421-427.
Abstract: The commonest mitochondrial diseases are probably those impairing the function of complex I of the respiratory electron transport chain. Such complex I impairment may contribute to various neurodegenerative disorders e.g. Parkinson's disease. In the following, using hepatocytes as a model cell, we have shown for the first time that the cytotoxicity caused by complex I inhibition by rotenone but not that caused by complex III inhibition by antimycin can be prevented by coenzyme Q (CoQ(1)) or menadione. Furthermore, complex I inhibitor cytotoxicity was associated with the collapse of the mitochondrial membrane potential and reactive oxygen species (ROS) formation. ROS scavengers or inhibitors of the mitochondrial permeability transition prevented cytotoxicity The CoQ(1) cytoprotective mechanism required CoQ (1) reduction by DT-diaphorase (NQO(1)). Furthermore, the mitochondrial membrane potential and ATIP levels were restored at low CoQ(1) concentrations (5 muM). This suggests that the CoQ(1)H(2) formed by NQO (1) reduced complex III and acted as an electron bypass of the rotenone block. However cytoprotection still occurred at higher CoQ(1) concentrations (>10 muM), which were less effective at restoring ATP

levels but readily restored the cellular cytosolic redox potential (i.e. lactate: pyruvate ratio) and prevented ROS formation. This suggests that CoQ(1) or menadione cytoprotection also involves the NQO(1) catalysed reoxidation of NADH that accumulates as a result of complex I inhibition. The CoQ(1)H(2) formed would then also act as a ROS scavenger.

Chanyachukul T, Yoovathaworn K, Thongsaard W, Chongthammakun S, Navasumrit P, Satayavivad J. 2004. Attenuation of paraquat-induced motor behavior and neurochemical disturbances by L-valine in vivo. Toxicol Lett 150(3):259-269.
Abstract: Alterations of motor behavioral patterns and monoamine contents in the discrete rat brain areas after acute paraquat exposure (3, 5, 10, 20 mg/kg, s.c.) have been studied. The results showed that paraquat at the doses of 5, 10, and 20 mg/kg significantly reduced locomotive, stereotypic, and rotational behaviors. Significant decreases of norepinephrine (NE) contents in cortex and hypothalamus, as well as striatal contents of dopamine (DA) and its acidic metabolites, were detected. In addition, L-valine (200 mg/kg, i.p.) significantly attenuated paraquat-induced toxicity at moderate dose (5 mg/kg) but not at high dose (20 mg/kg). The results provide evidence that paraquat can enter the brain as illustrated by the alterations in the motor behavioral pattern and neurochemical contents. Furthermore, the attenuation effect Of L-valine against systemic administration of paraquat-induced motor behaviors was detected, with a slightly protective effect on paraquat-induced neurochemical alterations. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Chapman LJ, Sauter SL, Henning RA, Levine RL, Matthews CG, Peters HA. 1991. Finger tremor after carbon disulfide-based pesticide exposures. Arch Neurol 48(8):866-870.
Abstract: Index finger tremor accompanying voluntary movement was studied in 19 age-matched control subjects and in 19 grain industry employees chronically exposed to carbon disulfide-based fumigants. Visual judgments of tremor amplitude made by neurologists during clinical examinations equaled the sensitivity of computerized tremor amplitude measurements. Tremor frequency variations detectable only with computerized measurement were present in grain workers with and without increased tremor amplitudes. Frequency differences discriminated between normal subjects and 74% of the grain workers. The distribution of tremor frequency power in the grain workers was often sequestered at 5 to 7 Hz, reminiscent of tremor in idiopathic Parkinson's disease. These findings suggest that the measurement of subtle tremor frequency changes may provide an early indication of chronic carbon disulfide poisoning.

Charalambous A, Mangner TJ, Kilbourn MR. 1995. Synthesis of (2-[c-11]methoxy) rotenone, a marker of mitochondrial complex-i activity. Nucl Med Biol 22 (1):65-69.
Abstract: Recent studies suggest that defects in the function of the complexes of the electron transport chain might be involved in the pathology of neurological diseases such as mitochondrial encephalopathies,

Parkinson's, Huntington's and Alzheimer's disease. Rotenone is a potent reversible competitive inhibitor of complex I (NADH-CoQ reductase). To study the possible involvement of complex I in such diseases, we synthesized (2-[C-11]methoxy)rotenone by [C-11]alkylation of 2-O-desmethyl rotenone methyl enol ether followed by hydrolysis of the enol ether to the ketone using aqueous trifluoroacetic acid. (2-[C-11]Methoxy) rotenone was purified by high pressure liquid chromatography (silica gel) and was obtained in 7-10% yields decay corrected to end of bombardment in synthesis times typically shorter than 48 min. Radiochemical purities were over 95% and specific activities averaged 1000 Ci/mmol at end of synthesis.

Charalambous A, Tluczek L, Frey KA, Higgins DS, Greenamyre TJ, Kilbourn MR. 1995. Synthesis and biological evaluation in mice of (2-[c-11]methoxy)-6', 7'-dihydrorotenol, a 2nd generation rotenoid for marking mitochondrial complex-i activity. Nucl Med Biol 22(4):491-496.
Abstract: Evidence has accumulated suggesting that impairment of the function of the complexes of the mitochondrial respiratory chain might be involved in the pathology of neurological diseases including Parkinson's and Huntington's diseases. Recently we reported the synthesis of (2-[C-11] methoxy)rotenone ([C-11]ROT) as a tool for in vivo studies of complex I. In an effort to develop a complex I imaging radiotracer which might be easier to synthesize and less likely to be metabolized, we prepared (2 [C-11]methoxy)-6',7'-dihydrorotenol([C-11]DHROT). The radiotracer was synthesized by [C-11]methylation of 2-O-desmethyl-6',7'-dihydrorotenol under basic [C-11]alkylation conditions. (2-[C-11]Methbxy)-6',7'-dihydrorotenol was produced in 30-35% radiochemical yields (decay corrected), with synthesis times shorter than 35 min. Radiochemical purities were over 95% and specific activities averaged 1000 Ci/mmol. The brain distributions of[C-11]ROT and [C-11]DHROT were investigated in mice after intravenous injections. For both radiotracers, distribution of radioactivity was similar in all brain regions examined. However, significantly higher uptake was observed with [C-11]DHROT than with [C-11]ROT, indicating that the alterations introduced in the structure of rotenone during the design of [C-11]DHROT resulted in a tracer with greater brain barrier permeability.

Checkoway H, Nelson LM. 1999. Epidemiologic approaches to the study of Parkinson's disease etiology. Epidemiology 10(3):327-336.
Abstract: The etiology of Parkinson's disease has been enigmatic to clinicians, epidemiologists, and basic scientists since the clinical syndrome was first described in 1817. Mendelian inheritance probably accounts fur a small proportion of Parkinson's disease. Apart from an increasing risk with age, the most consistent epidemiologic observation has been an inverse relation with cigarette smoking. Neither selective survival of nonsmokers nor behavioral characteristics of smokers can explain this seemingly protective association, interest in environmental exposures, particularly pesticides, metals, and industrial solvents, heightened substantially following the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a street drug contaminant, as a cause of human parkinsonism.

Epidemiologic and toxicologic research has since been guided to a great extent, although not exclusively, by mechanisms of MPTP toxicity. Efforts to characterize gene/environment interactions have also intensified in recent years. In this review, we evaluate recent evidence concerning the etiology of Parkinson's disease, with emphasis on environmental and lifestyle exposures and their potential interactions with genetic susceptibility traits. The most challenging aspects of epidemiologic research into Parkinson's disease causation include methodologic difficulties surrounding case definition, completeness of case ascertainment, selection of appropriate controls in case-control studies, and assessment of environmental exposures. We conclude with recommendations for future research directions.

Chen CJ, Liao SL. 2003. Zinc toxicity on neonatal cortical neurons: involvement of glutathione chelation. J Neurochem 85(2):443-453.
Abstract: Several mechanisms have been implicated in pathological neuronal death including zinc neurotoxicity, calcium excitotoxicity and oxidative injury. Glutathione (GSH) serves to provide reducing equivalents for the maintenance of oxidant homeostasis, and also plays roles in intracellular and intercellular signaling in the brain. We investigated the role of GSH homeostasis in the neurotoxic action of zinc using both mixed cortical cultures containing neurons and glia, and cortical neurons prepared from 1-day-old rats. Zinc caused neuronal cell death in a concentration-dependent manner. In parallel, a high concentration of zinc depleted GSH, in a time-dependent manner, preceding the onset of neuronal damage. Depletion of GSH by diethylmaleate injured neurons and exacerbated zinc-induced death. In contrast, replenishment of GSH attenuated zinc neurotoxicity. The thiol-containing compounds N -acetylcysteine and GSH chemically chelated zinc leading to decreases in the influx of zinc, the fall in GSH level and neuronal death. Interestingly, the glycolytic substrate pyruvate, but not lactate, chelated zinc concentration dependently and prevented its toxicity. On the other hand, pyrrolidine dithiocarbamate, serving as a zinc chaperon, enhanced its entry and toxicity. The results suggest that zinc non-enzymatically depleted GSH, an intrinsic factor for neuron survival, leading to activation of the cellular death signal and eventually neuronal death.

Chen J, Small-Howard A, Yin A, Berry MJ. 2005. The responses of Ht22 cells to oxidative stress induced by buthionine sulfoximine (BSO). BMC Neuroscience 6(1):10.
Abstract: Background: glutathione (GSH) is the most abundant thiol antioxidant in mammalian cells. It directly reacts with reactive oxygen species (ROS), functions as a cofactor of antioxidant enzymes, and maintains thiol redox potential in cells. GSH depletion has been implicated in the pathogenesis of neurological diseases, particularly to Parkinson's disease (PD). The purpose of this study was to investigate the change of cellular antioxidant status and basic cell functions in the relatively early stages of GSH depletion. Results: in this study, GSH was depleted by inhibition of glutamylcysteine synthetase using buthionine sulfoximine (BSO) treatment in Ht22, a neuronal cell line derived from mouse

hippocampus. Treatment with BSO produced dose-dependent decreases in total GSH level, Fe3+-reducing ability (FRAP assay), Cu2+- reducing ability (Antioxidant Potential, AOP assay), and ABTS free radical scavenging ability (ABTS assay) of the cells, but the sensitivity of these indicators to dosage varied considerably. Most of the changes were completed during the first 8 hours of treatment. Cell viability was tested by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromid) assay, and cells at lower density in culture were found to be more sensitive to GSH depletion. The activity of antioxidant enzymes, such as glutathione peroxidase (GPx), glutathione reductase (GR), and copper/zinc superoxide dismutase (Cu/Zn-SOD) were affected by GSH depletion. A cDNA expression array assay of the effects of BSO treatment showed significantly decreased mRNA level for 3 genes, and significantly increased mRNA level for 10 genes, including the antioxidant enzymes Cu/Zn-SOD and thioredoxin peroxidase 2 (TPxII). Conclusions: the study suggests that there are BSO-sensitive and BSO-resistant pools of GSH in Ht22 cells, and that different categories of antioxidant react differently to GSH depletion. Further, the effect of GSH status on cell viability is cell density dependent. Finally, the alterations in expression or activity of several antioxidant enzymes provide insight into the various cellular responses to GSH depletion.

Chen JY, Tsao GC, Zhao QQ, Zheng W. 2001. Differential cytotoxicity of Mn(II) and Mn(III): Special reference mitochondrial [Fe-S] containing enzymes. Toxicol Appl Pharmacol 175(2):160-168.
Abstract: Manganese (Mn)-induced neurodegenerative toxicity has been associated with a distorted iron (Fe) metabolism at both systemic and cellular levels. In the current study, we examined whether the oxidation states of Mn produced differential effects on certain mitochondrial [Fe-S] containing enzymes in vitro. When mitochondrial aconitase, which possesses a [4Fe-4S] cluster, was incubated with either Mn(II) or Mn(III), both Mn species inhibited the activities of aconitase. However, the IC10 (concentration to cause a 10% enzyme inhibition) for Mn(HI) was ninefold lower than that for Mn(II). Following exposure of mitochondrial fractions with Mn(II) or Mn(III), there was a significant inhibition by either Mn species in activities of Complex I whose active site contains five to eight [Fe-S] clusters. The dose-time response curves reveal that Mn(III) was more effective in blocking Complex I activity than Mn(II). Northern blotting was used to examine the expression of mRNAs encoding transferrin receptor (TfR), which is regulated by cytosolic aconitase. Treatment of cultured PC12 cells with Mn(II) and Mn(III) at 100 muM for 3 days resulted in 21 and 58% increases, respectively, in the expression of TfR mRNA. Further studies on cell growth dynamics after exposure to 25-50 muM Mn in culture media demonstrated that the cell numbers were much reduced in Mn(III)- treated groups compared to Mn(II)-treated groups, suggesting that Mn(III) is more effective than Mn(II) in cell killing. In cells exposed to Mn(II) and Mn(IH), mitochondrial DNA (mtDNA) was significantly decreased by 24 and 16%, respectively. In contrast, rotenone and MPP+ did not seem to alter mtDNA levels. These in vitro results suggest that Mn(IH) species appears to be more cytotoxic than Mn(II) species, possibly due to higher

oxidative reactivity and closer radius resemblance to Fe. (C) 2001 Academic Press.

Chen MJ, Yap YW, Choy MS, Koh CH, Seet SJ, Duan W, Whiteman M, Cheung NS. 2006 Jan 9. Early induction of calpains in rotenone-mediated neuronal apoptosis. Neurosci Lett .
Abstract: Rotenone is an inhibitor of mitochondrial complex I that produces a model of Parkinson's disease (PD), where neurons undergo apoptosis by caspase-dependent and/or caspase-independent pathways. Inhibition of calpains has recently been shown to attenuate neuronal apoptosis. This study aims to establish for the first time, the time-point of calpain activation with respect to the caspase activation and the possibility of cell cycle re-entry in rotenone-mediated cell death. Immunoblot results revealed calpain activation occurred at 5, 10h prior to caspase-3 activation (at 15h), suggesting calpain activation was an earlier cellular event compared to caspase activation in the rotenone-mediated apoptosis. In addition, an upregulation of phospho-p53 was observed at 21h. However, no expression or upregulation of cell cycle regulatory proteins including cdc25a, cyclin-D1 and cyclin-D3 were observed, strongly suggesting that cell cycle re-entry did not occur. These findings provide new insights into the differential patterns of calpain and caspase activation that result from rotenone poisoning and which may be relevant to the therapeutic management of PD.

Chen TS, Koutsilieri E, Rausch WD. 1995. Mpp(+) selectively affects calcium homeostasis in mesencephalic cell-cultures from embryonal c57/b16 mice. J Neural Transm Gen Sect 100(2):153-163.
Abstract: 1-Methyl-4-phenylpyridinium (MPP(+)), the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) serves as a valuable tool in animal models of Parkinson's disease. Primary cell cultures of mesencephalon from C57/B16 mice were used to investigate the effects of various dopaminergic neurotoxins on the intracellular calcium metabolism. MPP(+) ws compared to its precursor MPTP and a structural analogue paraquat (methylviologen). Direct addition of these neurotoxins (10 mu M) to fura-2-labeled cells did not change intracellular calcium concentrations ill the presence of 1 mM extracellular calcium. When mesencephalic neurons were exposed to the compounds for 24 hours, only MPP(+) led to an increase in calcium concentration in the absence and presence of extracellular calcium (36%, $p < 0.05$ and 47%, $p < 0.01$ versus control group). Intracellular calcium concentrations in cortical cultures devoid of dopaminergic cells were not changed by the above neurotoxins. Thus MPP (+) is shown to selectively increase intracellular calcium concentrations in mesencephalic cultures.

Cheng SY, Trombetta LD. 2004. The induction of amyloid precursor protein and alpha-synuclein in rat hippocarnpal astrocytes by diethyldithiocarbamate and copper with or without glutathione. Toxicol Lett 146(2):139-149.
Abstract: alpha-Synuclein is the major component of Lewy bodies. Its aggregation can be accelerated by copper, iron, or beta-amyloid (Abeta) and has been thought to provide a nucleation center during the formation

of amyloid plaques. The main structural component of amyloid plaque is Abeta, which is derived from a larger protein, amyloid precursor protein (APP). Xenobiotics have been implicated in the etiology of the neurodegenerative disease. Mechanisms of diethyldithiocarbamate (DDC) neurotoxicity involve copper chelation and interactions with SH groups resulting in oxidative stress. In this study, rat hippocampal astrocytes were treated with DDC (75 muM), CuCl2 (0.2 muM), or DDC (75 muM) Plus CuCl2 (0.2 muM) for 1 h. Cells were allowed to recover with or without 10 mM GSH. Results showed an increase of APP and alpha-synuclein production occurring in a time-dependent manner. At 4 h post-treatment, cells contained small positively stained material deposited throughout the cytosol for APP and by 8 h post-treatment increases were seen in both APP and alpha-synuclein. Immunoblots supported immunocytochemical results. Glutathione (GSH) decreased the accumulation of these proteins at 8 h post-treatment. (C) 2003 Elsevier Ireland Ltd. All rights reserved.

Chesrow EJ, Kaplitz SE, Bernstein M, Breme JT, Marquardt GH. 1966 Sep. Clinical evaluation of chlorphenesin carbamate (maolate) in spasticity, rigidity and pain associated with neurologic and arthritic diseases. J Am Geriatr Soc 14 (9):925-9.

Chetsawang B, Govitrapong P, Ebadi M. 2004. The neuroprotective effect of melatonin against the induction of c-Jun phosphorylation by 6-hydroxydopamine on SK-N-SH cells. Neurosci Lett 371(2-3):205-208.
Abstract: Melatonin is synthesized mainly in pineal gland. It has been suggested that melatonin has proven antioxidant effects and protective effects against neuronal cell degeneration. There are several studies indicating that c-Jun-N-terminal kinase pathways might be involved in neuronal cell death. In this study, the effects of melatonin on 6-hydroxydopamine (6-OHDA)-treated cultured SK-N-SH cells were investigated. The results showed that 6-OHDA significantly decreased cell viability as determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay, and melatonin was able to reverse the toxic effects of 6-OHDA on cell viability. In addition, induction of c-Jun phosphorylation by 6-OHDA was diminished by melatonin. These results demonstrate some protective properties of melatonin against neuronal cell degeneration and its action on the inhibition of c-Jun-N terminal kinase signaling cascade. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Chinopoulos C, Adam-Vizi V. 2001. Failure of in situ mitochondria to maintain membrane potential upon combined pesticide exposure and oxidative stress: implications for Parkinson's disease. J Neurochem 77:32.

Chinopoulos C, Adam-Vizi V. 2001. Mitochondria deficient in complex I activity are depolarized by hydrogen peroxide in nerve terminals: relevance to Parkinson's disease. J Neurochem 76(1):302-306.
Abstract: Deficiency of complex I in the respiratory chain and oxidative stress induced by hydrogen peroxide occur simultaneously in dopaminergic neurones in Parkinson's disease. Here we demonstrate that the membrane potential of in sif(I mitochondria (Delta Psim), as measured by the

fluorescence change of JC-I (5,5',6,6'-tetrachloro-1,1,3,3'-tetraethylbenzimidazolylcarbocyanine iodide), collapses when isolated nerve terminals are exposed to hydrogen peroxide (H2O2,100 and 500 muM) in combination with the inhibition of complex I by rotenone (5 nM-1 muM). H2O2 reduced the activity of complex I by 17%, and the effect of H2O2 and rotenone on the enzyme was found to be additive. A decrease in Delta Psim induced by H2O2 was significant when the activity of complex I was reduced to a similar extent as found in Parkinson's disease (26%). The loss of Delta Psim observed in the combined presence of complex I deficiency and H2O2 indicates that when complex I is partially inhibited, mitochondria in nerve terminals become more vulnerable to H2O2-induced oxidative stress. This mechanism could be crucial in the development of bioenergetic failure in Parkinson's disease.

Chinopoulos C, Tretter L, Adam-Vizi V. 1999. Depolarization of in situ mitochondria due to hydrogen peroxide-induced oxidative stress in nerve terminals: Inhibition of alpha-ketoglutarate dehydrogenase. J Neurochem 73(1):220-228.
Abstract: Mitochondrial membrane potential (Delta Psi(m)) was determined in intact isolated nerve terminals using the membrane potential-sensitive probe JC-1. Oxidative stress induced by H2O2 (0.1-1 mM) caused only a minor decrease in Delta Psi(m). When complex I of the respiratory chain was inhibited by rotenone (2 mu M), Delta Psi(m) was unaltered, but on subsequent addition of H2O2, Delta Psi(m) started to decrease and collapsed during incubation with 0.5 mM H2O2 for 12 min, The ATP level and [ATP]/[ADP] ratio were greatly reduced in the simultaneous presence of rotenone and H2O2. H2O2 also induced a marked reduction in Delta Psi (m) when added after oligomycin (10 mu M), an inhibitor of F0F1-ATPase. H2O2 (0.1 or 0.5 mM) inhibited alpha-ketoglutarate dehydrogenase and decreased the steady-state NAD(P)H level in nerve terminals. It is concluded that there are at least two factors that determine Delta Psi(m) in the presence of H2O2: (a) The NADH level reduced owing to inhibition of cu-ketoglutarate dehydrogenase is insufficient to ensure an optimal rate of respiration, which is reflected in a fall of Delta Psi(m) when the F0F1-ATPase is not functional. (b) The greatly reduced ATP level in the presence of rotenone and H2O2 prevents maintenance of Delta Psi(m) by F0F1-ATPase, The results indicate that to maintain Delta Psi(m) in the nerve terminal during H2O2-induced oxidative stress, both complex I and F0F1-ATPase must be functional. Collapse of Delta Psi(m) could be a critical event in neuronal injury in ischemia or Parkinson's disease when H2O2 is generated in excess and complex I of the respiratory chain is simultaneously impaired.

Choi DH, Kim DH, Park YG, Chun BG, Choi SH. 2002. Protective effects of rilmenidine and AGN 192403 on oxidative cytotoxicity and mitochondrial inhibitor-induced cytotoxicity in astrocytes. Free Radic Biol Med 33(10): 1321-1333.
Abstract: Oxidative stress and mitochondrial dysfunction are important aspects of pathogenesis, particularly in the brain, which is highly dependent on oxygen, and the protection of astrocytes is essential for

neuroprotection. In this context, imidazoline drugs have been reported to be neuroprotective. Our recent study showed that imidazoline drugs, including guanabenz, inhibit the naphthazarin-induced oxidative cytotoxicity associated with lysosomal destabilization. We now report on a study into the protective effects of rilmenidine and AGN 192403, which have affinity for imidazoline-1 receptors, on the cytotoxicity induced by naphthazarin and inhibitors of mitochondrial respiration in astrocytes. Cytotoxicity was measured grossly by LDH release and by measuring changes in lysosomal membrane stability and features of mitochondrial membrane permeabilization. Naphthazarin-induced cytotoxicity was evidenced by the ordered development of lysosomal acridine orange relocation, decrease in mitochondrial potential, cytochrome c release, and caspase-9 activation, and was inhibited by guanabenz, rilmenidine, and AGN 192403. Antimycin A and rotenone induced mitochondrial dysfunction primarily, and their cytotoxicities were inhibited only by AGN 192403. Rilmenidine and guanabenz may have a lysosomal stabilizing effect, which underlies their protective effects. AGN 192403 might affect the mitochondrial cell death cascades, and had a novel protective effect on the cytotoxicity associated with mitochondrial dysfunction. (C) 2002 Elsevier Science Inc.

Choi HJ, Lee SY, Cho Y, No H, Kim SW, Hwang O. 2005 Dec 9.
Tetrahydrobiopterin causes mitochondrial dysfunction in dopaminergic cells: Implications for Parkinson's disease. Neurochem Int .
Abstract: Parkinson's disease (PD) is a neurodegenerative disorder associated with a selective loss of dopaminergic neurons in the substantia nigra. While the underlying cause of PD is not clearly understood, oxidative stress and mitochondrial dysfunction are thought to play a role. We have previously suggested tetrahydrobiopterin (BH4), an obligatory cofactor for the dopamine synthesis enzyme tyrosine hydroxylase and present selectively in monoaminergic neurons in the brain, as an endogenous molecule that contributes to the dopaminergic neurodegeneration. In the present study, we show that BH4 leads to inhibition of activities of complexes I and IV of the electron transport chain (ETC) and reduction of mitochondrial membrane potential. BH4 appears to be different from rotenone and MPP(+), the synthetic compounds used to generate Parkinson models, in its effect on complex IV. BH4 also induces the release of mitochondrial cytochrome c. Pretreatment with the sulfhydryl antioxidant N-acetylcysteine or the quinone reductase inducer dimethyl fumarate prevents the ETC inhibition and cytochrome c release following BH4 exposure, suggesting the involvement of quinone products. Together with our previous observation that BH4 leads to generation of oxidative stress and selective dopaminergic neurodegeneration both in vitro and in vivo via inducing apoptosis, the mitochondrial involvement in BH4 toxicity further suggests possible relevance of this endogenous molecule to pathogenesis of PD.

Chrysostome V, Tison F, Yekhlef F, Sourgen C, Baldi I, Dartigues JF. 2004.
Epidemiology of multiple system atrophy: A prevalence and pilot risk factor study in Aquitaine, France. Neuroepidemiology 23(4):201-208.
Abstract: We investigated the prevalence of multiple system atrophy (MSA)

in Gironde, France, through a network of 120 public and private specialists and assessed the relationship between some environmental factors and MSA in a case-control study involving 50 MSA patients, 50 Parkinson's disease (PD) patients and 50 healthy controls. The occupational exposure to pesticides was evaluated through a job-exposure matrix. On prevalence day (November 1, 1998), the crude prevalence of MSA in Gironde was 1.94/100,000 inhabitants. We found no significant relationship between occupational exposure to pesticides and MSA. PD patients were significantly less frequently ever-smokers than controls and the same tendency was observed for MSA patients. We also described the clinical features that heralded the disease among this nonselected population. Copyright (C) 2004 S. Karger AG, Basel.

Chun HS, Gibson GE, Degiorgio LA, Zhang H, Kidd VJ, Son JH. 2001. Dopaminergic cell death induced by MPP+, oxidant and specific neurotoxicants shares the common molecular mechanism. J Neurochem 76 (4):1010-1021.
Abstract: Recent etiological study in twins (Tanner et al. 1999) strongly suggests that environmental factors play an important role in typical, non-familial Parkinson's disease (PD), beginning after age 50. Epidemiological risk factor analyses of typical PD cases have identified several neurotoxicants, including MPP+ (the active metabolite of MPTP), paraquat, dieldrin, manganese and salsolinol. Here, we tested the hypothesis that these neurotoxic agents might induce cell death in our nigral dopaminergic cell line, SN4741 (Son et al 1999) through a common molecular mechanism. Our initial experiments revealed that treatment with both MPP + and the other PD-related neurotoxicants induced apoptotic cell death in SN4741 cells, following initial increases of H2O2-related ROS activity and subsequent activation of JNK1/2 MAP kinases. Moreover, we have demonstrated that during dopaminergic cell death cascades, MPP+, the neurotoxicants and an oxidant, H2O2 equally induce the ROS-dependent events. Remarkably, the oxidant treatment alone induced similar sequential molecular events: ROS increase, activation of JNK MAP kinases, activation of the PITSLRE kinase, p110, by both Caspase-1 and Caspase-8-like activities and apoptotic cell death. Pharmacological intervention using the combination of the antioxidant Trolox and a pan-caspase inhibitor Boc-(Asp)-fmk (BAF) exerted significant neuroprotection against ROS-induced dopaminergic cell death. Finally, the high throughput cDNA microarray screening using the current model identified downstream response genes, such as heme oxygenase-1, a constituent of Lewy bodies, that can be the useful biomarkers to monitor the pathological conditions of dopaminergic neurons under neurotoxic insult.

Chung KKK, Dawson VL, Dawson TM. 2003. New insights into Parkinson's disease. J Neurol 250:15-24.
Abstract: Parkinson's disease (PD) is the most common neurodegenerative movement disorder. Recent advances in genetics and pathophysiology have led to new insights into the pathogenesis of PD. Ten loci have been linked to hereditary PD. Mutations in alpha-synuclein and ubiquitin carboxy hydrolase L1 (UchL1) cause autosomal dominant PD and mutations in

parkin and DJ-1 cause autosomal recessive PD. alpha-Synuclein has emerged as an important protein in the pathogenesis of PD, as it appears to be the major structural component of Lewy bodies and its accumulation/ aggregation seems to play a prominent role in sporadic PD. Mutations in parkin are the most common cause of hereditary PD, and mutations in parkin are thought to lead to a loss of parkin's ubiquitin E3 ligase activity. Derangements in parkin function as well as mutations in UCH-L1 fit with the notion that derangements in the ubiquitin proteasomal pathway (UPP) may play important roles in the demise of dopamine neurons in PD. DJ-1 is a protein of unknown function that is linked to autosomal recessive PD. Oxidative stress and impairment in mitochondrial complex I activity are important in sporadic PD, and there is emerging interest in the role of herbicides, fungicides and insecticides that inhibit mitochondrial complex I activity and their role in contributing to the development of PD. These important findings serve as the foundation for discovering new pathways that may lead to the development of new therapies for PD.

Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, Gross RE. 2005. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiol Dis 20(2):360-371.
Abstract: In recent years, several lines of evidence have shown an increase in Parkinson's disease (PD) prevalence in rural environments where pesticides are widely used. Paraquat (PQ-herbicide) and maneb (MB-fungicide) are among the compounds suspected to induce neuronal degeneration and motor deficits characteristics of PD. Here, we investigated the effects of PQ and NIB on dopaminergic (DA) neuron-glia cultures and in vivo in young adult rats. In vitro, PQ led to a loss of DA as compared to non-DA neurons and microglial activation in a dose-dependent manner. Addition of NIB had no further effect nor did it lead to microglial activation when used alone. In vivo, 2-month old young adult rats were subjected to intraperitoneal injections of vehicle (n = 4), PQ alone (n = 8), or PQ in combination with NIB (n = 8) twice a week for 4 weeks and were sacrificed the day following the last injection. Significant loss of nigral DA neurons was observed in both treatment groups, but a significant decrease in striatal DA fibers was not found. Microglial activation was seen in the nigra of rats subjected to PQ with or without MB. Behavioral analyses demonstrated a mixed pattern of motor impairments, which may have been related to early effects of nigral DA neuronal loss or systemic effects associated with NIB exposure in addition to PQ. These results indicate that exposure to PQ with or without NIB induces neuro degeneration which might occur via an early inflammatory response in young adult animals. (c) 2005 Elsevier Inc. All rights reserved.

Clarimon J, Eerola J, Hellstrom I, Tienari PJ, Singleton A. 2004. Paraoxonase 1 (PON1) gene polymorphisms and Parkinson's disease in a Finnish population. Neurosci Lett 367(2):168-170.
Abstract: Paraoxonase 1 (PON1) is involved in the metabolism and detoxification of insecticides and pesticides. Two polymorphisms within the gene affect the enzyme activity. One is a methionine to leucine change at position 54 (M54L) and the other is a glutamine to arginine variant at

position 192 (Q192R). There are contrasting reports assessing the role of these variants in Parkinson's disease (PD). We performed a case-control association study in order to elucidate the possible contribution of variability within PON1 to the risk of sporadic PD in a Finnish population. There was no statistically significant association of the allele, genotype or haplotype distribution with PD (all P values > 0.75). Our results suggest that the M54L and Q192R polymorphisms are not major risk factors for PD in the Finnish population. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Clayton R, Clark JB, Sharpe M. 2005. Cytochrome c release from rat brain mitochondria is proportional to the mitochondrial functional deficit: implications for apoptosis and neurodegenerative disease. J Neurochem 92 (4):840-849.
Abstract: Apoptosis may be initiated in neurons via mitochondrial release of the respiratory protein, cytochrome c. The mechanism of cytochrome c release has been studied extensively, but little is known about its dynamics. It has been claimed that release is all-or-none, however, this is not consistent with accumulating evidence of cytosolic mechanisms for 'buffering' cytochrome c. This study has attempted to model an underlying disease pathology, rather than inducing apoptosis directly. The model adopted was diminished activity of the mitochondrial respiratory chain complex I, a recognized feature of Parkinson's disease. Titration of rat brain mitochondrial respiratory function, with the specific complex I inhibitor rotenone, caused proportional release of cytochrome c from isolated synaptic and non-synaptic mitochondria. The mechanism of release was mediated, at least in part, by the mitochondrial outer membrane component Bak and voltage-dependent anion channel rather than non-specific membrane rupture. Furthermore, preliminary data were obtained demonstrating that in primary cortical neurons, titration with rotenone induced cytochrome c release that was subthreshold for the induction of apoptosis. Implications for the therapy of neurodegenerative diseases are discussed.

Coghlan A. 2005. Exposure to pesticides can cause Parkinson's. New Scientist 186(2501):14.

Collins MA, Neafsey EJ. 2002. Potential neurotoxic "agents provocateurs" in Parkinson's disease. Neurotoxicol Teratol 24(5):571-577.
Abstract: Idiopathic Parkinson's disease (PD), one of the most common neurodegenerative disorders associated with aging, is characterized neurochemically by abnormal and profound loss of nigrostriatal dopamine (DA) neurons. A prominent current view is that the excessive degeneration of the dopaminergic system is the outcome of extended insults by environmental neurotoxins or endogenous neurotoxic factors in genetically vulnerable or susceptible individuals. Recent insights into the identities and mechanisms of potential neurotoxic species, which span pesticides, environmental contaminants including heterocyclic amines with beta-carboline (betaC) and isoquinoline (IQ) structures, endogenous DA metabolites or intermediates, neuromelanin, metals, and infectious agents,

are presented. (C) 2002 Elsevier Science Inc. All rights reserved.

Conn KJ, Gao WW, Ullman MD, Mckeon-O'malley C, Eisenhauer PB, Fine RE, Wells JM. 2002. Specific up-regulation of GADD153/CHOP in 1-methyl-4-phenyl-pyridinium-treated SH-SY5Y cells. J Neurosci Res 68(6):755-760.
Abstract: Growth arrest DNA damage-inducible 153 (GADD153) expression was increased in 1-methyl-4-phenyl-pyridinium (MPP+)-treated human SH-SY5Y neuroblastoma cells as determined by gene microarray analysis. GADD153 expression increased after 24 hr of MPP+ (1 mM) exposure and preceded activation of caspase 3. Comparison of GADD153 expression among cultures treated with other toxins whose primary mode of action is either via mitochondrial impairment (rotenone) or via oxidative stress (6-hydroxydopamine or hydrogen peroxide) showed that GADD153 was uniquely up-regulated by MPP+. Together these data suggest that a cellular mechanism distinct from mitochondrial impairment or oxidative stress contributes significantly to the upregulation of GADD153 by MPP+ and that GADD153 may function as an inducer of apoptosis following MPP-exposure. Published 2002 Wiley-Liss, Inc.

Conn KJ, Ullman MD, Larned MJ, Eisenhauer PB, Fine RE, Wells JM. 2003. CDNA microarray analysis of changes in gene expression associated with MPP+ toxicity in SH-SY5Y cells. Neurochem Res 28(12):1873-1881.
Abstract: cDNA microarray analysis of 1-methyl-4-phenyl-pyridinium (MPP +) toxicity (1 mM, 72 h) in undifferentiated SH-SY5Y cells identified 48 genes that displayed a signal intensity greater than the mean of all differentially expressed genes and a two-fold or greater difference in normalized expression. RT-PCR analysis of a subset of genes showed that c-Myc and RNA-binding protein 3 (RMB3) expression decreased by similar to50% after 72 h of exposure to MPP+ (1 mM) but did not change after 72 h of exposure to 6-hydroxydopamine (25 muM), rotenone (50 nM), and hydrogen peroxide (600 muM). Exposure of retinoic acid (RA)-differentiated SH-SY5Y cells to MPP+ (1 mM, 72 h) also resulted in a decrease in RMB3 expression and an increase in GADD153 expression. In contrast, c-Myc expression was slightly increased in RA-differentiated cells. Collectively, these data provide new insights into the molecular mechanisms of MPP+ toxicity and show that MPP+ can elicit distinct patterns of gene expression in undifferentiated and RA-differentiated SH-SY5Y cells.

Cooper JM, Schapira AHV. 1997. Mitochondrial dysfunction in neurodegeneration. J Bioenerg Biomembr 29(2):175-183.
Abstract: Numerous toxins are known to interfere with mitochondrial respiratory chain function. Use has been made of these in the development of pesticides and herbicides, and accidental use in man has led to the development of animal models for human disease. The propensity for mitochondrial toxins to induce neuronal cell death may well reflect not only their metabolic pathways but also the sensitivity of neurons to inhibition of oxidative phosphorylation. Thus, the accidental exposure of humans to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and to 3-nitropropionic acid has led to primate models of Parkinson's disease and Huntington's disease,

respectively. These models were made all the more remarkable when identical biochemical deficiencies were identified in relevant areas of humans suffering from the respective idiopathic diseases. The place of complex I deficiency in Parkinson's disease remains undetermined, but there is recent evidence to suggest that, in some cases at least, it may play a primary role. The complex II/III deficiency in Huntington's disease is likely to be secondary and induced by other pathogenetic factors. The potential to intervene in the cascade of reactions involving mitochondrial dysfunction and cell death offers prospects for the development of new treatment strategies either for neuroprotection in prophylaxis or rescue.

Corasaniti MT, Nistico G. 1993. Determination of paraquat in rat-brain by high-performance liquid-chromatography. J Chromatogr 643(1-2):419-425.
Abstract: The applications of a method based on ion-pair solid-phase extraction and reversed-phase HPLC are reported. The method was used to measure paraquat concentrations in discrete brain areas at different times after its systemic administration in rats. In addition, the method was employed in the determination of paraquat levels in whole-brain samples from rats of various ages systemically treated with several doses of the herbicide.

Corasaniti MT, Strongoli MC, Rotiroti D, Bagetta G, Nistico G. 1998. Paraquat: A useful tool for the in vivo study of mechanisms of neuronal cell death. Pharmacology & Toxicology 83(1):1-7.
Abstract: The present article reviews the results of experimental studies on paraquat neurotoxicity, started by our group several years ago - when clinical and experimental reports had increased the interest for the possibility that environmental chemicals, including paraquat, may be related to the development of Parkinson's disease -, and which are still continuing since paraquat appears to be a promising tool to study the mechanisms of neuronal cell death in vivo. Our observations have demonstrated that paraquat causes evident neurotoxic effects after intracerebroventricular or intracerebral injection in experimental animals; however, it seems that the herbicide does not exibit a selective neurotoxicity towards the dopaminergic nigro-striatal system since potent behavioural and electrocortical changes are induced by paraquat after injection in brain areas other than the substantia nigra and caudate nucleus. By studying the mechanisms through which paraquat induces neurotoxic effects in vivo, it was shown that either free radical production and activation of cholinergic and glutamatergic transmission may be regarded as related events which play a crucial role in paraquat-induced neurotoxicity. In addition, it was observed that in rats paraquat penetrates the blood-brain barrier following systemic administration to give rise to a differential brain regional distribution; the latter observation rises some concern over the hazard of paraquat as a potential environmental neurotoxin. Indeed, paraquat, administered systemically in rats produces behavioural excitation and brain damage. The brain damage appears to be selective for the pyriform cortex and this does not seem to be strictly related to the high concentrations reached by the herbicide in this area but to the higher vulnerability of this cortical area to the enhanced cholinergic

transmission. The recent observation that paraquat, injected into the rat hippocampus, induces the expression of apoptotic neuronal cell death, appears of valuable interest also with a view to paraquat as an useful experimental model in the development of neuroprotective drugs able to block the molecular events which, once activated, are responsible for the induction of neuronal cell death.

Coria F, Castano EM, Frangione B. 1987 Dec. Brain amyloid in normal aging and cerebral amyloid angiopathy is antigenically related to Alzheimer's disease beta-protein. Am J Pathol 129(3):422-8.
Abstract: Amyloid deposition is a prominent feature of a number of brain disorders, in which amyloid fibrils are found within blood vessel walls, the neuropil (neuritic plaques), neurons (neurofibrillary tangles). These include Alzheimer's disease (AD), AD changes associated with Down's syndrome, neurologically asymptomatic amyloidosis, Parkinson dementia of Guam, hereditary cerebral hemorrhage with amyloidosis of Icelandic origin (HCHWA-I), hereditary cerebral hemorrhage with amyloidosis of Dutch origin (HCHWA-D), and sporadic cerebral amyloid angiopathy (SCAA). Recently it was shown that the amyloid deposits in AD, Parkinson dementia of Guam, and HCHWA-D are formed by a similar 4-kd polypeptide called beta-protein. Because the nature of the amyloid deposits in other types of cerebral amyloidosis is not known, we have conducted immunocytochemical studies on brains from autopsy cases of AD, HCHWA-D, SCAA and neurologically asymptomatic elderly individuals. Brains from two subjects without neurologic involvement were used as controls. Sections from these specimens were incubated with rabbit polyclonal antibodies against 1) a synthetic peptide of 28 residues (anti-SP28), homologous to the NH2-terminal sequence of the beta-protein, 2) the main amyloid component of the HCHWA-I, a variant of cystatin C, and 3) purified fraction of neurofibrillary tangles. In all cases, anti-SP28 antibody specifically stained amyloid deposits in leptomeningeal and cortical vessels and neuritic plaques. These findings demonstrate that the amyloid deposits of SCAA and aged brains are composed of a protein antigenically similar to AD, HCHWA-D, and Parkinson dementia of Guam beta-protein, suggesting that all of these clinically and etiologically different morbid conditions are pathogenetically related. On this basis, they can be tentatively grouped as beta-protein deposition diseases. In addition, we found that HCHWA-D and SCAA vessels were mainly affected, while in AD parenchymal involvement predominates. These differences in the localization and extent of beta-protein deposits may account from the predominance of vascular complications in HCHWA-D and SCAA and of dementia in AD.

Cormier A, Morin C, Zini R, Tillement JP, Lagrue G. 2003. Nicotine protects rat brain mitochondria against experimental injuries. Neuropharmacology 44 (5):642-652.
Abstract: Epidemiological studies have reported that cigarette smoking may protect from neurodegenerative diseases such as Parkinson's disease. These protective effects are thought to be mediated by nicotine. Recent data showed that nicotine significantly decreases respiratory control ratio (RCR) and superoxide anion generation of brain mitochondria. Thus, we

investigated nicotine effects on rat brain in two experimental models: first, an in vitro anoxia/reoxygenation experiment and secondly, an in vivo rotenone-induced Parkinson-like syndrome. Anoxia/reoxygenation impaired mitochondrial respiration by 43.68% whereas in the presence of nicotine, it was less impaired, by 31.1% at 10(-7) M. In rats chronically administered rotenone (3 mg/kg/day), we observed profound mitochondrial damage: the RCR decreased by 50.36% and the superoxide anion generation and the membrane anisotropy increased by 56.03 and 13.43%, respectively. All of these indications of mitochondrial damage were limited by chronic administration of nicotine. Nicotine developed mitochondrial effects in vivo and in vitro at very low concentration. All these results were in accordance with epidemiological studies, which report a protective effect of nicotine in neurodegenerative diseases. Thus, we propose that one effect of nicotine is to preserve mitochondrial functions of the rat central nervous system. (C) 2003 Elsevier Science Ltd. All rights reserved.

Corrigan FM, French M, Murray L. 1996. Organochlorine compounds in human brain. Human & Experimental Toxicology 15(3):262-264.
Abstract: Having observed polychlorinated biphenyls (PCBs) in brain tissue obtained post mortem from two men we have carried out a study of organochlorine compounds in frontal cortex from patients with Parkinson's disease (PD) and from controls. No PCBs were found in any of those samples. There was no difference in the concentration of the DDT metabolite pp'-DDE in the PD brain samples. Dieldrin (HEOD) was significantly decreased in PD brain when analysed by lipid weight. While these findings would not support the hypothesis that PCBs may contribute to the development of Parkinson's disease in humans it remains possible that they may cause damage to the basal ganglia before being displaced from brain tissue.

Corrigan FM, Murray L, Wyatt CL, Shore RF. 1998. Diorthosubstituted polychlorinated biphenyls in caudate nucleus in Parkinson's disease. Exp Neurol 150(2):339-342.
Abstract: As it had previously been demonstrated that there were reduced brain dopamine concentrations in monkeys who had been given polychlorinated biphenyls (PCBs) chronically, we hypothesized that organochlorine compounds in general, and PCBs in particular might be important in the pathogenesis of Parkinson's disease (PD). In a study of caudate nucleus obtained post mortem from patients with Parkinson's disease and from controls, there were significantly higher concentrations of the organochlorine insecticide dieldrin and the PCB congener 153 in the PD tissue. DDE, PCB congener 180, and total PCBs (matched with a commercial preparation) also tended to be higher in Parkinson's disease tissue. We think that this is important preliminary evidence that diorthosubstituted PCBs may contribute to the pathogenesis of Parkinson's disease, and a greater presence of organochlorine insecticides in the PD tissue suggests that this may be in part the explanation for the association between PD and rural living. (C) 1998 Academic Press.

Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D. 2000. Organochlorine insecticides in substantia nigra in Parkinson's disease. Journal of Toxicology and Environmental Health-Part a 59(4):229-234.
Abstract: The concentrations of organochlorine (OC) compounds in the substantia nigra (SN) were compared in Parkinson's disease (PD) with concentrations in brain from cortical Lewy body dementia (CLBD), Alzheimer's disease (AD), and nondemented nonparkinsonian controls (CON). The levels of the gamma isomer of hexachlorocyclohexane (gamma HCH, lindane) were significantly higher in PD tissues (mean +/- SD: 0.56 +/- 0.434 mu g/g lipid) than in the other three groups (CLBD 0.052 +/- 0. 101 mu g/g lipid; AD none detected; CON 0.125 +/- 0.195: all differences from PD significant at p < .05, Mann-Whitney U-test). Dieldrin (HEOD) was higher in PD brain than in AD or control brain, while 1, 1'-(2,2-dichloroethenyl diene)-bis(4-chlorobenzene) (p,p-DDE) and total Aroclor-matched polychlorinated biphenyls (matched PCBs) were only higher in PD substantia nigra when these concentrations were compared with those of CLBD. These findings are not inconsistent with the hypothesis derived from epidemiological work and animal studies that organochlorine insecticides produce a direct toxic action on the dopaminergic tracts of the substantia nigra and may contribute to the development of PD in those rendered susceptible by virtue of cytochrome P-450 polymorphism, excessive exposure, or other factors.

Cory-Slechta DA. 2005. Studying toxicants as single chemicals: Does this strategy adequately identify neurotoxic risk? Neurotoxicology 26(4): 491-510.
Abstract: Despite the fact that virtually all chemicals exposure of humans are to mixtures, and that these mixed exposures occur in the context of numerous other risk modifiers, our current understanding of human health risks is based almost entirely on the evaluation of chemicals studied in isolation. This paper describes findings from our collaborative studies that prompt questions about these approaches in the context of neurotoxicology. The first section describes studies investigating the interactions of maternal Pb exposure with maternal stress. Examined across a range of outcome measures, it shows that maternal Pb can modulate the effects of maternal stress, and, conversely, stress modifies the effects of Pb. Further effects of Pb + stress could be detected in the absence of an effect of either risk factor alone, and, moreover, the profile of effects of Pb alone differs notably from that of Pb + stress. Collectively, interactions were not systematic, but differed by brain region, gender and outcome measure. A second section describes outcomes of studies examining combined exposures to the pesticides paraquat (PQ) and munch (MB) during development which likewise reveal potentiated effects of combined exposures. They also demonstrate examples of both progressive and cumulative neurotoxicity, including a marked vulnerability following gestational exposure to MB, to the effects of PQ, a pesticide with no structural relationship to MB. The ability of current hazard identification and risk assessment approaches to adequately identify and encompass such effects remains an important unanswered question. One consideration

proposed for further evaluating potential interactions that may be of significance for the nervous system is based on a multi-hit hypothesis. It hypothesizes that the brain may readily compensate for the effects of an individual chemical itself acting on a particular target system, but when multiple target or functional sites within that one system are attacked by different mechanisms (i.e., multiple chemical exposures or chemical exposures combined with other risk factors), homeostatic capabilities may be restricted, thereby leading to sustained or cumulative damage. (c) 2005 Elsevier Inc. All rights reserved.

Cory-Slechta DA, Thiruchelvam M, Barlow BK, Richfield EK. 2005. Developmental pesticide models of the Parkinson disease phenotype. Environ Health Perspect 113(9):1263-1270.
Abstract: It has been hypothesized that developmental insults could contribute to Parkinson disease (PD), a neurodegenerative disorder resulting from the loss of the dopamine neurons of the nigrostriatal pathway. Two models of developmental pesticide exposures in mice are presented here that yield PD phenotypes consistent with this possibility. Combined exposures to the herbicide paraquat (PQ) and the fungicide maneb (MB), both of which adversely affect dopamine systems, administered from postnatal days 5-19, produced selective losses of dopamine and metabolites and reduced numbers of dopamine neurons in the substantia nigra. Effects were greater than those produced by adult-only exposures. Moreover, developmental PQ + MB exposures enhanced vulnerability to this pesticide regimen when administered subsequently in adulthood. In a second model, exposure to MB from gestational days 10-17 markedly increased vulnerability to PQ exposures during adulthood, with reductions in dopamine and metabolites and numbers of dopamine neurons in the substantia nigra. Females evidenced protection in both models. Collectively, these models demonstrate that developmental exposures can produce progressive, permanent, and cumulative neurotoxicity of the nigrostriatal dopamine system and enhance vulnerability to subsequent environmental insults. Finally, effects of PQ + MB were greater than those of either pesticide alone in the postnatal model. This is consistent with a multiple-hit hypothesis predicting that multiple concurrent insults occurring at different target sites within a system (here nigrostriatal dopamine) may constrict the range and flexibility of compensatory mechanisms, thereby compromising the integrity and viability of the system. As such, this hypothesis presents a biologic strategy for identifying potentially significant neurotoxic mixtures for hazard identification in future studies.

Cory-Slechta DA, Thiruchelvam M, Richfield EK, Barlow BK, Brooks AI. 2005. Developmental pesticide exposures and the Parkinson's disease phenotype. Birth Defects Research Part a-Clinical and Molecular Teratology 73(3):136-139.
Abstract: Whereas Parkinson's disease is a neurodegenerative disorder that typically onsets after 60 years of age, the possibility that it could result from insults sustained during development has been proposed. Experimental evidence based on the combined paraquat + maneb model of the Parkinson's disease (PD) phenotype summarized here provides support

for such an assertion. Postnatal exposures of mice to these pesticides led not only to a permanent and selective loss of dopaminergic neurons in the substantia nigra pars compacta but also enhanced the impact of these pesticides administered during adulthood relative to developmental only or adult only treatment. Exposure to maneb alone during gestation resulted in a dramatic response to paraquat in adulthood, including notable reductions in levels of dopamine and metabolites and a loss of nigral dopamine (DA) neurons, despite the fact that paraquat does not share structural similarity to or mechanisms of action with maneb. Collectively, these studies provide developmental environmental models of the PD phenotype. In addition, they demonstrate the fact that silent neurotoxicity produced by developmental insults can be unmasked by challenges later during life as well as the potential for cumulative neurotoxicity over the life span. (c) 2005 Wiley-Liss, Inc.

Cory-Sletcha DA, Thiruchelvam M, Richfield EK, Brooks I. 2003. Developmental pesticide exposure and the Parkinson's Disease phenotype. Pediatr Res 53 (6):11A.

Costa LG, Richter RJ, Li WF, Cole T, Guizzetti M, Furlong CE. 2003. Paraoxonas (PON1) as a biomarker of susceptibility for organophosphate toxicity. Biomarkers 8(1):1-12.
Abstract: Paraoxonase (PON1) is an A-esterase capable of hydrolysing the active metabolites (oxons) of a number of organophosphorus (OP) insecticides such as parathion, diazinon and chlorpyrifos. PON1 activity is highest in liver and plasma, and among animal species significant differences exist, with birds and rabbits displaying very low and high activity, respectively. Human PON1 has two polymorphisms in the coding region (Q192R and L55M) and five polymorphisms in the promoter region. The Q192R polymorphism imparts different catalytic activity toward some OP substrates, while the polymorphism at position -108 (C/T) is the major contributor to differences in the level of PON1 expression. Animal studies have shown that PON1 is an important determinant of OP toxicity, with animal species with a low PON1 activity having an increased sensitivity to OPs. Administration of exogenous PON1 to rats or mice protects them from the toxicity of OPs. PON1 knockout mice display a high sensitivity to the toxicity of diazoxon and chlorpyrifos oxon, but not paraoxon. In vitro assayed catalytic efficiencies of purified PON192 isoforms for hydrolysis of specific oxon substrates accurately predict the degree of in vivo protection afforded by each isoform. Low PON1 activity may also contribute to the higher sensitivity of newborns to OP toxicity.

Coulom H, Birman S. 2004. Chronic exposure to rotenone models sporadic Parkinson's disease in Drosophila melanogaster. J Neurosci 24(48): 10993-10998.
Abstract: Parkinson's disease (PD) is a movement disorder characterized by the selective degeneration of nigrostriatal dopaminergic neurons. Both familial and sporadic cases present tremor, rigidity, slowness of movement, and postural instability. Although major insights into the genes responsible for some rare hereditary cases have arisen, the etiology of

sporadic cases remains unknown. Epidemiological studies have suggested an association with environmental toxins, mainly mitochondrial complex I inhibitors such as the widely used pesticide rotenone. In recent years, Drosophila melanogaster has been used as a model of several neurodegenerative diseases, including a genetic model of PD. Here, we studied the neurodegenerative and behavioral effects of a sublethal chronic exposure to rotenone in Drosophila. After several days, the treated flies presented characteristic locomotor impairments that increased with the dose of rotenone. Immunocytochemistry analysis demonstrated a dramatic and selective loss of dopaminergic neurons in all of the brain clusters. The addition of L-dopa (3,4-dihydroxy-L-phenylalanine) into the feeding medium rescued the behavioral deficits but not neuronal death, as is the case in human PD patients. In contrast, the antioxidant melatonin (N-acetyl-5-methoxytryptamine) alleviated both symptomatic impairment and neuronal loss, supporting the idea that this agent may be beneficial in the treatment of PD. Therefore, chronic exposure to pesticides recapitulates key aspects of PD in Drosophila and provides a new in vivo model for studying the mechanisms of dopaminergic neurodegeneration.

Cox B, Tha SJ. 1975 Feb. Amantadin e tremor, a 5-hydroxytryptamine-mediated response? Eur J Pharmacol 30(2):344-51.
Abstract: Amantadine-induced tremor has been investigated using mice. Experiments with, mebanazine, reserpine, diethyldithiocarbamate, and p-chlorophenylalanine suggest that the tremorgenic action of amantadine is influenced by a balance between three putative central nervous system (CNS) transmitters: noradrenaline, dopamine and 5-hydroxytryptamine (5-HT). Drugs which reduce the concentration of the catecholamines in brain increase amantadine induced tremor. p-Chlorophenylalanine, which specifically depletes brain 5-HT, antagonises amantadine-induced tremor. An ED50 (tremor) dose of amantadine decreases the concentration of 5-hydroxy-indoleacetic acid (5-HIAA) in rat brain, particularly when this elevated due to pretreatment with 5-hydroxytryptophan. Neither inhibition of monoamine oxidase nor reduction of 5-HT-reuptake appear to be responsible for this decrease. Experiments on rat fundus suggest that amantadine increased the sensitivity of receptors to 5-HT. A similar mechanism of action in the CNS could explain both the tremor and the decrease in brain 5-HIAA. The possible relevance of these findings is discussed with respect to the known anti-Parkinson action of amantadine.

Cutillas B, Espejo M, Ambrosio S. 1998. 7-nitroindazole prevents dopamine depletion caused by low concentrations of MPP+ in rat striatal slices. Neurochem Int 33(1):35-40.
Abstract: A significant loss of dopamine was found in rat striatal slices incubated with 1-methyl-4-phenylpyridinium ion (MPP+) at a concentration of 2 mu M or higher. The addition of 7-nitroindazole, a specific inhibitor of neuronal nitric oxide synthase (nNOS), prevented this effect on dopamine when the concentration of MPP+ was between 2-5 mu M, but not at higher concentrations. This protection was reproduced with other less specific NOS-inhibitors, such as nitro-arginine and nitro-arginine methylester. 7-nitroindazole did not protect against the dopamine depletion caused by the

non-specific mitochondrial chain blocker rotenone. Neither MPP+ nor rotenone significantly increased the nitrite concentration in striatal slices, measured as an index of nitric oxide production. The basal production of nitric oxide may be enough to trigger the dopamine depletion at very low concentrations of MPP+, probably acting synergistically with cytosolic calcium increase. Higher concentrations of MPP+ are toxic by themselves without the mediation of nitric oxide. The inhibition of nNOS may protect against dopamine loss at early stages of a neurodegenerative process, and it could then be considered in the treatment or prevention of neurodegenerative human processes such as Parkinson's disease. (C) 1998 Elsevier Science Ltd. All rights reserved.

Da Costa MDL, Goncalves LR, Barbosa ER, Bacheschi LA. 2003. Neuroimaging abnormalities in parkinsonism: study of five cases . Arq Neuropsiquiatr 61 (2B): 381-386.
Abstract: We report the brain magnetic resonance (MR) imaging abnormalities observed at the basal ganglia system of 5 patients (2 female and 3 male), who fulfilled the criteria of parkinsonism. The onset of parkinsonian syndrome ranged from 5 to 52 years old. All patients underwent MR exams with a 1.5T MR equipment. High field T2-weighted sequences disclosed hypersignal bilateral and symmetrically located exclusively at substantia nigra (3 cases), exclusively at globus pallidus (1 case) and simultaneously at substantia nigra, globus pallidus and nigro-strital interconnections (1 case). For three patients, the diagnose of secondary parkinsonism was supported by clinical data: the first had the onset of the symptoms after the exposure to an herbicide (glyphosate); the second after vaccination against measles; the third after coma due to encephalitis. For the other two patients, the onset of PS was progressive, resembling a typical idiopathic Parkinson's disease (PD) but the findings at the MR dimissed this initial diagnose. In this study, the contribution of neuroimaging was crucial to recognize secondary parkinsonism though the ethiological agents could not be determined in these patients.

Dagani F, Ferrari R, Anderson JJ, Chase TN. 1991. L-dopa does not affect electron-transfer chain enzymes and respiration of rat muscle mitochondria. Mov Disord 6(4):315-319.
Abstract: Alterations in mitochondrial respiratory chain enzymes have been found in skeletal muscle of parkinsonian patients. Most of these patients had received treatment with L-dopa in combination with an inhibitor of peripheral decarboxylase for several years. In order to determine whether these effects are only dependent on the disease or are partially due to its therapy, the effects of L-dopa methyl ester and benserazide, a peripheral dopa decarboxylase inhibitor, were studied on various parameters related to energy metabolism in rat skeletal muscle mitochondria. The maximum activities related to complexes of the respiratory chain: rotenone-sensitive NADH-cytochrome c reductase, succinate-cytochrome c reductase, cytochrome c oxidase, state 3, state 4, uncoupled state, and respiratory control ratio were measured after 17-19 days of treatment. The results indicate that L-dopa treatment does not interfere with any of the parameters investigated and suggest that changes in muscle mitochondrial

function found in parkinsonian patients are the result of the disease process and not its treatment.

Dalfo E, Gomez-Isla T, Rosa JL, Bodelon MN, Tejedor MC, Barrachina M, Ambrosio S, Ferrer I. 2004. Abnormal alpha-synuclein interactions with rab proteins in alpha-synuclein A30P transgenic mice. J Neuropathol Exp Neurol 63(4):302-313.
Abstract: Mutation A30P in the a-synuclein gene is a cause of familial Parkinson disease. Transgenic mice expressing wild mouse and mutant human A30P alpha-synuclein, Tg5093 mice (Tg), show a progressive motor disorder characterized by tremor, rigidity, and dystonia, accompanied by accumulation of alpha-synuclein in the soma and neurites and by a conspicuous gliosis beginning in the hippocampal formation at the age of 7 to 8 months and spreading throughout the CNS. Impaired short-term changes in synaptic strength have also been documented in hippocampal slices from Tg mice. alpha-synuclein aggregates of approximately 34 and 70 kDa, in addition to the band of 17 kDa, corresponding to the molecular weight of a-synuclein, were recovered in the PBS-soluble fraction of brain homogenates from Tg mice but not from brain samples from age-matched wildtype littermates. MPTP-treated Tg and wildtype mice produced alpha-synuclein aggregates in the PBS-, deoxycholate-, and SDS-soluble fractions. Aggregates of alpha-synuclein, although with different molecular weights, were also observed in rotenone-treated Tg and wildtype mice. Pull-down studies with members of the Rab protein family have shown that a-synuclein from Tg mice interacts with Rab3a, Rab5, and Rab8. This binding is not due to the amount of alpha-synuclein (levels of which are higher in Tg mice) and it is not dependent on the amount of Rab protein used in the assay. Rather, alpha-synuclein interactions with Rab proteins are due to mutant (x-synuclein as demonstrated in Rab pull-down assays with recombinant of wildtype and mutant A30P human alpha-synuctein. Since Rab3a, Rab5, and Rab8 are important proteins involved in synaptic vesicle trafficking and exocytosis at the synapse, vesicle endocytosis, and trans-Golgi transport, respectively, it can be suggested that these functions are impaired in Tg mice. This rationale is consistent with previous data showing that short-term hippocampal synaptic plasticity is altered and that a.-synuclein accumulates in the cytoplasm of neurons in Tg mice.

Darios F, Corti O, Lucking CB, Hampe C, Muriel MP, Abbas N, Gu WJ, Hirsch EC, Rooney T, Ruberg M, Brice A. 2003. Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. Hum Mol Genet 12(5):517-526.
Abstract: Parkin gene mutations have been implicated in autosomal-recessive early-onset parkinsonism and lead to specific degeneration of dopaminergic neurons in midbrain. To investigate the role of Parkin in neuronal cell death, we overproduced this protein in PC12 cells in an inducible manner. In this cell line, neuronally differentiated by nerve growth factor, Parkin overproduction protected against cell death mediated by ceramide, but not by a variety of other cell death inducers (H2O2, 4-hydroxynonenal, rotenone, 6-OHDA, tunicamycin, 2-mercaptoethanol and staurosporine). Protection was abrogated by the proteasome inhibitor

epoxomicin and disease-causing variants, indicating that it was mediated by the E3 ubiquitin ligase activity of Parkin. Interestingly, Parkin acted by delaying mitochondrial swelling and subsequent cytochrome c release and caspase-3 activation observed in ceramide-mediated cell death. Subcellular fractionation demonstrated enrichment of Parkin in the mitochondrial fraction and its association with the outer mitochondrial membrane. Together, these results suggest that Parkin may promote the degradation of substrates localized in mitochondria and involved in the late mitochondrial phase of ceramide-mediated cell death. Loss of this function may underlie the degeneration of nigral dopaminergic neurons in patients with Parkin mutations.

Davey GP, Clark JB. 1996. Threshold effects and control of oxidative phosphorylation in nonsynaptic rat brain mitochondria. J Neurochem 66(4): 1617-1624.
Abstract: The amount of control exerted by respiratory chain complexes in isolated nonsynaptic mitochondria prepared from rat brain on the rate of oxygen consumption was assessed using inhibitor titrations. Rotenone, myxothiazol, and KCN were used to titrate the activities of NADH:ubiquinone oxidoreductase (EC 1.6.5.3; complex I), ubiquinol:ferrocytochrome c oxidoreductase (EC 1.10.2.2; complex III), and cytochrome c oxidase (EC 1.9.3.1; complex IV), respectively. Complexes I, III, and IV shared some of the control of the rate of oxygen consumption in nonsynaptic mitochondria, having flux control coefficients of 0.14, 0.15, and 0.24, respectively. Threshold effects in the control of oxidative phosphorylation were demonstrated for complexes I, III, and IV. It was found that complex I activity could be decreased by similar to 72% before major changes in mitochondrial respiration and ATP synthesis took place. Similarly, complex III and IV activities could be decreased by similar to 70 and 60%, respectively, before major changes in mitochondrial respiration and ATP synthesis occurred, These results indicate that previously observed decreases in respiratory chain complex activities in some neurological disorders need to be reassessed as these decreases might not affect the overall capability of nonsynaptic mitochondria to maintain energy homeostasis unless a certain threshold of decreased complex activity has been reached. Possible implications for synaptic mitochondria and neurodegenerative disorders are also discussed.

Davis KL, Yesavage JA, Berger PA. 1978. Possible organophosphate-induced parkinsonism. J Nerv Ment Dis 166(3):222-225.

De Sarno P, Shestopal SA, King TD, Zmijewska A, Song L, Jope RS. 2003. Muscarinic receptor activation protects cells from apoptotic effects of DNA damage, oxidative stress, and mitochondrial inhibition. J Biol Chem 278 (13):11086-11093.
Abstract: The impact of muscarinic receptor stimulation was examined on apoptotic signaling induced by DNA damage, oxidative stress, and mitochondrial impairment. Exposure of human neuroblastoma SH-SY5Y cells to the DNA-damaging agent camptothecin increased p53 levels, activated caspase-3, and caused cell death. Pretreatment with

oxotremorine-M, a selective agonist of muscarinic receptors that are expressed endogenously in these cells, did not affect the accumulation of p53 but greatly attenuated caspase-3 activation and protected from cell death to nearly the same extent as treatment with a general caspase inhibitor. Treatment with 50-200 muM H2O2 caused the activation of caspase-3 beginning after 2-3 h, followed by eventual cell death. Oxotremorine-M pretreatment protected cells from H2O2-induced caspase-3 activation and death, and this was equivalent to protection afforded by a caspase inhibitor. Muscarinic receptor stimulation also protected cells from caspase-3 activation induced by exposure to rotenone, a mitochondrial complex 1 inhibitor, but no protection was evident from staurosporine-induced caspase-3 activation. The mechanism of protection afforded by muscarinic receptor activation from camptothecin-induced apoptotic signaling involved blockade of mitochondrial cytochrome c release associated with a bolstering of mitochondrial bcl-2 levels and blockade of the translocation of Bax to mitochondria. Likely the most proximal of these events to muscarinic receptor activation, mitochondrial Bax accumulation, also was attenuated by oxotremorine-M treatment after treatment with H2O2 or rotenone. These results demonstrate that stimulation of muscarinic receptors provides substantial protection from DNA damage, oxidative stress, and mitochondrial impairment, insults that may be encountered by neurons in development, aging, or neurodegenerative diseases. These findings suggest that neurotransmitter-induced signaling bolsters survival mechanisms, and inadequate neurotransmission may exacerbate neuronal loss.

Debbarh I, Rambelomanana S, Penouil F, Castaigne F, Poisot D, Moore N. 2002. Human neurotoxicity of ethylene-bis-dithiocarbamates (EBDC). Rev Neurol (Paris) 158(12):1175-1180.
Abstract: Ethylene-bis-dithiocarbamates (EBDC) (maneb, mancozeb,...) are fungicides which rarely cause acute toxicity reactions, but may have a severe long-term toxic effect. Twelve cases reported to the Bordeaux Anti-Poison Center over a 10-year period generally exhibited short-term neurological symptoms of variable severity. Cases of acute intoxication reported in the literature have involved various neurological signs including headache, dizziness and confusion, and a few cases of seizures, all of which were rapidly reversible. Long-term exposure has been associated with parkinsonism, and epidemiological studies have found an increased risk of neurocognitive impairment associated with long-term exposure to pesticides in general and to EBDC specifically. Experimentally, EBDC increases the neurotoxicity of MPTP and paraquat. Their metabolite, ethylene thiourea (ETU), is neurotoxic in utero. There are indications that EBDC and/or ETU may increase sensitivity to genetic and environmental risk factors for cell death and apoptosis. Occupational or accidental exposure to EBDC and its possible long-term consequences require adequate studies concerning their mechanism, surveillance and prevention.

Deng H, Jankovic J, Guo Y, Xie WJ, Le WD. 2005. Small interfering RNA targeting the PINK1 induces apoptosis in dopaminergic cells SH-SY5Y. Biochem Biophys Res Commun 337(4):1133-1138.

Abstract: PTEN-induced kinase 1 (PINKJ) is a recently identified gene, mutations of which cause levodopa-responsive parkinsonism. An overexpression of wild-type PINK1 protects neurons from stress-induced mitochondrial dysfunction and apoptosis. We studied the effects of PIAIK1 suppression using small interfering RNA (siRNA), which call inhibit PINK1 mRNA expression up to 87%,, and decrease PINKI protein up to 80% in human dopaminergic cell line SH-SY5Y. Incubation with PINKI siRNA decreased SH-SY5Y cell viability and significantly increased MPP+ or rotenone-induced cytotoxicity. Our results indicate that reduction in PINK1 expression call trigger apoptotic process that can be exacerbated by the presence of MPP+ or rotenone. These findings support the hypothesis that PINK1 participates in the protection of dopaminergic neurons. (c) 2005 Elsevier Inc. All rights reserved.

Deng YF, Newman B, Dunne MP, Silburn PA, Mellick GD. 2004. Further evidence that interactions between CYP2D6 and pesticide exposure increase risk for Parkinson's disease. Ann Neurol 55(6):897.

Denton T, Howard BD. 1987 Aug. A dopaminergic cell line variant resistant to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. J Neurochem 49 (2):622-30.
Abstract: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to cause parkinsonism by killing dopaminergic neurons; the toxic substance is a metabolite, 1-methyl-4-phenylpyridinium ion (MPP+). PC12 cells, which are dopaminergic, are killed in culture by MPTP and MPP+ but at concentrations much higher than that required to kill affected neurons in vivo. However, at low concentrations (10-100 microM), MPP+ caused an increased production of lactate by PC12 cells. MPP+-treated PC12 cells exhibited decreased mitochondrial respiration. Mitochondria from the treated cells respired normally in the presence of added succinate but not beta-hydroxybutyrate, a finding indicating that MPP+ inhibits the oxidation of some substrates selectively. MPP+ was more effective in killing the cells when glycolysis was reduced with 2-deoxyglucose or by lowering the glucose content of the culture medium. Under these conditions, MPP+ inhibited ATP synthesis and depleted cellular stores of ATP. A PC12 variant that is even more resistant to MPTP and MPP+ than are wild-type cells has been isolated. The MPTP-resistant variant is also more resistant to the lethal effects of oligomycin, antimycin A, and rotenone. This variant exhibited altered lactate production and mitochondrial respiration. It is suggested that some brain neurons that accumulate MPP+ without being killed by it may also have an energy metabolism somewhat different from that of more sensitive neurons.

Desai AK, Grossberg GT. 2005 Sep. Rivastigmine for Alzheimer's disease. Expert Rev Neurother 5(5):563-80.
Abstract: Alzheimer's disease is the most common form of neurodegenerative dementia and poses considerable health challenges to both patients and their families. Rivastigmine is a powerful slow-reversible, noncompetitive carbamate cholinesterase inhibitor that is approved for the treatment of mild-to-moderate Alzheimer's disease. Randomized, double-

blind, placebo-controlled trials of up to 6 months duration have shown beneficial effects of rivastigmine compared with placebo in measures of cognition and global functioning. Less rigorous but growing data suggest that the beneficial effects may endure for up to 5 years, extend to more advanced stages of Alzheimer's disease and may occur in noncognitive domains, such as activities of daily living and the behavioral symptoms of Alzheimer's disease. Evidence from controlled studies also supports the use of rivastigmine for cognitive and behavioral symptoms in Alzheimer's disease associated with vascular risk factors, dementia with Lewy bodies and Parkinson's disease dementia. Early and continued treatment of Alzheimer's disease with rivastigmine maximizes the observed beneficial effects. The most prominent adverse effect of rivastigmine is centrally mediated cholinergic gastrointestinal events, which can be minimized by slower dose-escalation intervals and administration with a full meal. Therapeutic dosing is 6-12 mg/day given twice daily, with higher doses having the potential for greater benefits.

Deshpande SS, Smith CD, Filbert MG. 1995. Assessment of primary neuronal culture as a model for soman-induced neurotoxicity and effectiveness of memantine as a neuroprotective drug. Arch Toxicol 69(6):384-390.
Abstract: An in vitro mammalian model neuronal system to evaluate the intrinsic toxicity of soman and other neurotoxicants as well as the efficacy of potential countermeasures was investigated. The link between soman toxicity, glutamate hyperactivity and neuronal death in the central nervous system was investigated in primary dissociated cell cultures from rat hippocampus and cerebral neocortex. Exposure of cortical or hippocampal neurons to glutamate for 30 min produced neuronal death in almost 80% of the cells examined at 24h. Hippocampal neurons exposed to soman for 15-120 min at 0.1 mu M concentration caused almost complete inhibition ( greater than or equal to 90%) of acetylcholinesterase but failed to show any evidence of effects on cell viability, indicating a lack of direct cytotoxicity by this agent. Acetylcholine (ACh, 0.1mM), alone or in combination with soman, did not potentiate glutamate toxicity in hippocampal neurons. Memantine, a drug used for the therapy of Parkinson's disease, spasticity and other brain disorders, significantly protected hippocampal and cortical neurons in culture against glutamate and N-methyl-D-aspartate (NMDA) excitotoxicity. In rats a single dose of memantine (18 mg/kg) administered 1 h prior to a s.c. injection of a 0.9 LD (50) dose of soman reduced the severity of convulsions and increased survival. Survival, however, was accompanied by neuronal loss in the frontal cortex, piriform cortex and hippocampus.

Destee A. 2003. Neuroprotection and neurodegenerative parkinsonian syndromes. Rev Neurol (Paris) 159(5):S93-S104.
Abstract: The diffuse nature of the lesions in neurodegenerative parkinsonian syndromes explains the inefficacy of symptomatic treatments and the potential interest of neuroprotector treatments that could slow down or even prevent neuron degeneration in structures involved in the degenerative processes. As these syndromes share preferential degeneration of the substantia nigra with Parkinson's disease it is logical to

hypothesize that the same mechanisms of neuron death are involved. The responsibility of an exotoxin, with a mechanism of action that would be similar to that of MPTP and/or rotenone, appears to be implicated only in progressive supranuclear palsy (PSP): this is suggested by the "guadeloupean parkinsonean" syndrome. There is no evidence demonstrating an exotoxin in corticobasal degeneration (CBD), which might play an anecdotal role in rare cases of multiple system atrophy (MSA). There are rare cases of PSP, sometimes with autopsy proof, generally with autosomal dominant inheritance, but in the much larger number of sporadic cases there is an undeniable genetic susceptibility linked with certain polymorphisms of the tau protein gene. Genetic susceptibility plays a much less pronounced role in CBD. There is no argument however in favor of a genetic factor in MSA. A few arguments suggest that oxidative stress is involved in PSP and MSA, or even CBD, but no evidence of a primary effect. Perturbed mitochondrial metabolism is possible in PSP. Undeniable proof of the effect of inflammation, excitotoxicity, and apoptosis remains to be presented. We now have several compounds which could affect different phases of neurodegeneration. Identifying the precise cause of neuronal death is needed to properly choose the most effective therapeutic approach (single drug or multiple drug regimens). Therapeutic assessment should be conducted in patients with certain diagnosis. This apparently evident prerequisite does not however appear to be easy to satisfy as has been demonstrated by anatomoclinical series in PSP and MSA, and even more so in CBD. Use of international criteria does not alleviate the difficulty. Satisfactory criteria of efficacy remain to be identified. Assuming that such trials would be conclusive, there remains the question of how to implement neuroprotection in routine practice. The difficulties encountered are well known: late intervention after development of the disease in sporadic cases, ethical issues concerning preclinical screening in familial forms of the disease or in patients exposed to an exotoxin.

Destee A. 2003 May. [Neuroprotection and neurodegenerative parkinsonian syndromes]. Rev Neurol (Paris) 159(5 Pt 2):3S93-104.
Abstract: The diffuse nature of the lesions in neurodegenerative parkinsonian syndromes explains the inefficacy of symptomatic treatments and the potential interest of neuroprotector treatments that could slow down or even prevent neuron degeneration in structures involved in the degenerative processes. As these syndromes share preferential degeneration of the substantia nigra with Parkinson's disease it is logical to hypothesize that the same mechanisms of neuron death are involved. The responsibility of an exotoxin, with a mechanism of action that would be similar to that of MPTP and/or rotenone, appears to be implicated only in progressive supranuclear palsy (PSP): this is suggested by the "guadeloupean parkinsonean" syndrome. There is no evidence demonstrating an exotoxin in corticobasal degeneration (CBD), which might play an anecdotal role in rare cases of multiple system atrophy (MSA). There are rare cases of PSP, sometimes with autopsy proof, generally with autosomal dominant inheritance, but in the much larger number of

sporadic cases there is an undeniable genetic susceptibility linked with certain polymorphisms of the tau protein gene. Genetic susceptibility plays a much less pronounced role in CBD. There is no argument however in favor of a genetic factor in MSA. A few arguments suggest that oxidative stress is involved in PSP and MSA, or even CBD, but no evidence of a primary effect. Perturbed mitochondrial metabolism is possible in PSP. Undeniable proof of the effect of inflammation, excitotoxicity, and apoptosis remains to be presented. We now have several compounds which could affect different phases of neurodegeneration. Identifying the precise cause of neuronal death is needed to properly choose the most effective therapeutic approach (single drug or multiple drug regimens). Therapeutic assessment should be conducted in patients with certain diagnosis. This apparently evident prerequisite does not however appear to be easy to satisfy as has been demonstrated by anatomoclinical series in PSP and MSA, and even more so in CBD. Use of international criteria does not alleviate the difficulty. Satisfactory criteria of efficacy remain to be identified. Assuming that such trials would be conclusive, there remains the question of how to implement neuroprotection in routine practice. The difficulties encountered are well known: late intervention after development of the disease in sporadic cases, ethical issues concerning preclinical screening in familial forms of the disease or in patients exposed to an exotoxin.

Dexter DT, Sian J, Rose S, Hindmarsh JG, Mann VM, Cooper JM, Wells FR, Daniel SE, Lees AJ, Schapira AH, et al. 1994 Jan. Indices of oxidative stress and mitochondrial function in individuals with incidental Lewy body disease. Ann Neurol 35(1):38-44.
Abstract: Brain tissue from normal individuals with incidental Lewy bodies and cell loss in pigmented substantia nigra neurons (asymptomatic Parkinson's disease) and age-matched control subjects without nigral Lewy bodies was examined biochemically. There was no difference in dopamine levels or dopamine turnover in the caudate and putamen of individuals with incidental Lewy body disease compared to control subjects. There were no differences in levels of iron, copper, manganese, or zinc in the substantia nigra or other brain regions from the individuals with incidental Lewy body disease compared to those from control subjects. Similarly, ferritin levels in the substantia nigra and other brain areas were unaltered. There was no difference in the activity of succinate cytochrome c reductase (complexes II and III) or cytochrome oxidase (complex IV) between incidental Lewy body subjects and control subjects. Rotenone-sensitive NADH coenzyme Q1 reductase activity (complex I) was reduced to levels intermediate between those in control subjects and those in patients with overt Parkinson's disease, but this change did not reach statistical significance. The levels of reduced glutathione in substantia nigra were reduced by 35% in patients with incidental Lewy body disease compared to control subjects. Reduced glutathione levels in other brain regions were unaffected and there were no changes in oxidized glutathione levels in any brain region. Altered iron metabolism is not detectable in the early stages of nigral dopamine cell degeneration. There may be some impairment of

mitochondrial complex I activity in the substantia nigra in Parkinson's disease.(ABSTRACT TRUNCATED AT 250 WORDS)

Di Angelantonio S, Bernardi G, Mercuri NB. 2004. Methamidophos transiently inhibits neuronal nicotinic receptors of rat substantia nigra dopaminergic neurons via open channel block. Neurosci Lett 369(3):208-213.
Abstract: The use of acetylcholinesterase (AChE) inhibitors is the primary therapeutic strategy in the treatment of Alzheimer's disease. However, these drugs have been reported to have effects beyond the simple stimulation of neuronal acetylcholine receptors (AChRs) by elevated acetylcholine (ACh), interfering directly with the nAChR. Therefore, a pure pharmacological blockade of AChE is not usually obtained. In this study, the patch-clamp technique was utilized to determine the effects of methamidophos, a pesticide that is considered a selective AChE inhibitor, on nAChRs of substantia nigra dopaminergic neurons. In spite of the fact that methamidophos has been reported to be devoid of direct nicotinic actions, our main observation was that it selectively and reversibly blocked nAChR responses, without directly affecting the holding current. Methamidophos produced a downward shift in the dose response curve for nicotine; the mechanism accounting for this non-competitive antagonism was open channel block, in view of its voltage dependence. Pre-treatment with vesamicol did not prevent the reduction of nicotine-induced currents, indicating that the effect on nAChRs was independent from the activity of methamidophos as a cholinesterase inhibitor. Our results conclude that methamidophos has a complex blocking action on neuronal nAChRs that is unlinked to the inhibition of AChE. Therefore, it should not be considered a selective AChE inhibitor and part of its toxic effects could reside in an interference with the nicotinic neurotransmission. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Di Monte DA. 2001. The role of environmental agents in Parkinson's disease. Clinical Neuroscience Research 1(6):419-426.
Abstract: Experimental, clinical and epidemiological evidence indicates that exposure to environmental agents may contribute to the pathogenesis of Parkinson's disease (PD). The development of animal models of toxicant-induced nigrostriatal injury has furthered our understanding of mechanisms of neurodegeneration and will help us to identify compounds or classes of compounds as potential PD risk factors. Examples are rodent models utilizing the pesticides paraquat or rotenone. Important implications for PD are also likely to arise from knowledge of synergistic environmental interactions (e.g. the paraquat/maneb model), as well as relationships between exogenous and endogenous factors. In particular, the endogenous protein a-synuclein, recently linked to PD pathophysiology. could play an important role in the neurodegenerative process triggered by toxicant exposure. (C) 2001 Elsevier Science B.V. All rights reserved.

Di Monte DA. 2003. The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? Lancet Neurology 2(9): 531-538.
Abstract: Recent epidemiological and experimental studies have renewed

interest in the hypothesis that the environment has a role in the pathogenesis of Parkinson's disease (PD). Epidemiological studies have identified protective associations (eg, smoking) as well as adverse risk factors leg, pesticide exposure) for PD. The concordance rate of PD in pairs of dizygotic twins is similar to that in pairs of monozygotic twins, supporting a role of non-genetic risk factors. New models of selective nigrostriatal damage-such as neurotoxicity induced by rotenone or paraquat-have emphasised that environmental agents may contribute to the neuroclegenerative process in PD. Toxins interact, in vitro and in vivo, with alpha-synuclein, an endogenous protein that is implicated in pathology of PD. Similarities between clinical and experimental findings, such as the role of pesticide exposure as a potential environmental risk factor, highlight the importance of a multidisciplinary approach to the aetiology of PD.

Di Monte DA, Lavasani M, Manning-Bog AB. 2002. Environmental factors in Parkinson's disease. Neurotoxicology 23(4-5):487-502.
Abstract: Evidence discussed in this review article lends strong support in favor of an etiologic role of environmental factors in Parkinson's disease. First, thanks to the discovery of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), it is now clear that, by targeting the nigrostriatal system, neurotoxicants can reproduce the neurochemical and pathological features of idiopathic parkinsonism. The sequence of toxic events triggered by MPTP has also provided us with intriguing clues concerning mechanisms of toxicant selectivity and nigrostriatal vulnerability. Relevant examples are (i) the role of the plasma membrane dopamine transporter in facilitating the access of potentially toxic species into dopaminergic neurons; (ii) the vulnerability of the nigrostriatal system to failure of mitochondrial energy metabolism; and (iii) the contribution of inflammatory processes to tissue lesioning. Epidemiological and experimental data suggest the potential involvement of specific agents as neurotoxicants (e.g. pesticides) or neuroprotective compounds (e.g. tobacco products) in the pathogenesis of nigrostriatal degeneration, further supporting a relationship between the environment and Parkinson's disease. A likely scenario that emerges from our current knowledge is that neurodegeneration results from multiple events and interactive mechanisms. These may include (i) the synergistic action of endogenous and exogenous toxins (e.g. the ability of the pesticide diethyldithiocarbamate to promote the toxicity of other compounds); (ii) the interactions of toxic agents with endogenous elements (e.g. the protein alpha-synuclein); (iii) the tissue response to an initial toxic insult; and, last but not least, (iv) the effects of environmental factors on the background of genetic predisposition and aging. (C) 2002 Elsevier Science Inc. All rights reserved.

Di Monte DA, Tokar I, Langston JW. 1999. Impaired glutamate clearance as a consequence of energy failure caused by MPP+ in astrocytic cultures. Toxicol Appl Pharmacol 158(3):296-302.
Abstract: Astrocytes are the site of bioactivation of the parkinsonism-inducing agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into its toxic 1-methyl-4-phenylpyridinium (MPP+) metabolite. The mechanism by which MPP+ is capable of decreasing astrocytic glutamate uptake was

evaluated in this study using primary cultures of astrocytes. Addition of glutamate to these cultures was followed by its efficient clearance from the extracellular space. However, when astrocytes were preincubated with MPP +, glutamate clearance was significantly impaired. This effect was concentration-dependent, became more pronounced by prolonging the incubation in the presence of MPP+ and occurred at a time when cell membrane integrity was still preserved. No evidence was found that reactive oxygen species contributed to MPP+-induced decrease in glutamate clearance. Indeed, neither the spin trapping agent alpha-phenyl-tert-butyl nitrone, the lazaroid antioxidant U-74389G, nor the disulfide-reducing agent dithiothreitol was capable of restoring glutamate net uptake. The effect of MPP+ on glutamate clearance: (i) was accompanied by a decrease in cellular ATP; (ii) could be enhanced by withdrawing glucose from the incubation medium or by inhibiting glycolysis with 2-deoxyglucose, and (iii) could be reproduced using the mitochondrial complex I inhibitor rotenone. Taken together, these results indicate that, by acting as a mitochondrial poison, MPP+ impairs energy metabolism of astrocytes and significantly reduces their ability to maintain low levels of extracellular glutamate. (C) 1999 Academic Press.

Diaz-Corrales FJ, Asanuma M, Miyazaki I, Miyoshi K, Ogawa N. 2005. Rotenone induces aggregation of gamma-tubulin protein and subsequent disorganization of the centrosome: Relevance to formation of inclusion bodies and neurodegeneration. Neuroscience 133(1):117-135.
Abstract: Neurodegenerative disorders are characterized by progressive loss of specific neurons in the central nervous system. Although they have different etiologies and clinical manifestations, most of them share similar histopathologic characteristics such as the presence of inclusion bodies in both neurons and glial cells, which represent intracellular aggregation of misfolded or aberrant proteins. In Parkinson's disease, formation of inclusion bodies has been associated with the aggresome-related process and consequently with the centrosome. However, the significance of the centrosome in the neurodegenerative process remains obscure. In the present study, the morphological and functional changes in the centrosome induced by rotenone, a common insecticide used to produce experimental Parkinsonism, were examined both in vitro and in vivo. Aggregation of gamma-tubulin protein, which is a component of the centrosome matrix and recently identified in Lewy bodies of Parkinson's disease, was observed in primary cultures of mesencephalic cells treated with rotenone. Rotenone-treated neurons and astrocytes showed enlarged and multiple centro-somes. These centrosomes also displayed multiple aggregates of alpha-synuclein protein. Neurons with disorganized centrosomes exhibited neurite retraction and microtubule destabilization, and astrocytes showed disturbances of mitotic spindles. The Golgi apparatus, which is closely related to the centrosome, was dispersed in both rotenone-treated neuronal cells and the substantia nigra of rotenone-treated rats. Our findings suggested that recruitment of abnormal proteins in the centrosome contributed to the formation of inclusion bodies, and that rotenone markedly affected the structure and function of the centrosome with

consequent induction of cytoskeleton disturbances, disassembly of the Golgi apparatus and collapse of neuronal cells. (c) 2005 IBRO. Published by Elsevier Ltd. All rights reserved.

Diaz-Corrales FJ, Asanuma M, Miyazaki I, Ogawa N. 2004. Rotenone induces disassembly of the Golgi apparatus in the rat dopaminergic neuroblastoma B65 cell line. Neurosci Lett 354(1):59-63.
Abstract: It has been reported that the Golgi apparatus (GA) is fragmented in some neurodegenerative diseases. However, the significance of the GA fragmentation or disassembly in neurodegeneration is still obscure. To clarify the involvement of this organelle in apoptosis of neuronal cells, we examined the morphological changes in the GA induced by rotenone, a pesticide that produces selective dopaminergic neurodegeneration. In dopaminergic neuroblastoma B65 cells, a 5-day rotenone treatment (50 nM) promoted cell damage. Rotenone-treated cells showed round nuclei, diffuse signals of the GA and cytosolic redistribution of cytochrome c. Nevertheless, these type of cells without nuclear fragmentation did not show any caspase-3 expression. These results indicate that rotenone induces disassembly of the GA in the early stages of the apoptotic process. (C) 2003 Elsevier Ireland Ltd. All rights reserved.

DiMatteo K. 2004 Nov. Pesticides and organic agriculture. Environ Health Perspect 112(15):A865; discussion A865.

Donaire V, Niso M, Moran JM, Garcia L, Gonzalez-Polo RA, Soler G, Fuentes JM. 2005. Heat shock proteins protect both MPP+ and paraquat neurotoxicity. Brain Res Bull 67(6):509-514.
Abstract: The exposure of immortalized rat neuroblast cells to MPP+ and paraquat results in cell death. Heat shock pre-treatment prior to the addition of MPP+ and paraquat significantly reduced cell death and led to an increase in the synthesis of Hsp27 and Hsp70 proteins. Quercetin inhibits the synthesis of heat shock proteins (Hsp) and prevents their protective effect, which suggests that this protection was dependent on the Hsps synthesis. These data indicate that heat shock protects cells from the toxic effect of MPP+ and paraquat. These results and the structural similarity between paraquat and MPP+ support the role of paraquat as a putative risk factor in the etiology of Parkinson's disease. (c) 2005 Elsevier Inc. All rights reserved.

Dow J, Piriou F, Wolf E, Dulery BD, Haegele KD. 1994. Novel carbamate metabolites of mofegiline, a primary amine monoamine-oxidase-b inhibitor, in dogs and humans. Drug Metabolism and Disposition 22(5): 738-749.
Abstract: Mofegiline or MDL 72,974A ((E)-4-fluoro-beta-fluoromethylene benzene butanamine hydrochloride) is a selective enzyme-activated irreversible inhibitor of monoamine oxidase B, which is under development for use in the treatment of Parkinson's disease. Male beagle dogs were given single po (20 mg/kg) and iv (5 mg/kg) doses of [C-14]-Mofegiline. Total radioactivity excreted in urine and feces over 96 hr was, respectively, 75.5 +/- 3.8 and 6.3 +/- 3.4% of the dose after po and 67.9

+/- 0.5 and 3.9 +/- 2.4% after iv administration. Unchanged drug in urine represented 3% of the dose after po and less than 1% after iv administration. Mofegiline was thus extensively metabolized in dogs, and urinary excretion was the major route of elimination of metabolites. HPLC, with on-line radioactivity detection, showed the presence of four major peaks (M(1), M(2), M(3), and M(4)), representing respectively 50, 9, 5, and 0.5% of the administered dose excreted in 0-24 hr urine. TSP-LC-MS, FAB MS, and NMR spectra of the purified metabolites were obtained. M(1), the major metabolite in dogs, was shown to have undergone defluorination of the beta-fluoromethylene moiety, and one carbon addition. Its structure was confirmed to be a cyclic carbamate. M(2) was a N-carbamoyl O-beta-D-glucuronide conjugate of parent drug. The formation of M(1) and M(2) is likely to involve initial reversible addition of CO2 to the primary amine function. M(3) was a N-succinyl conjugate of the parent drug. M(4) had also undergone defluorination to yield a urea adduct of an unsaturated alpha, beta aldehyde. Structures of M(1) end M(3) were further confirmed by comparing their MS and NMR spectra with those of authentic reference compounds. TSP-LC-MS ion chromatograms of human urine, obtained from two male volunteers after po administration of 24 mg of drug, showed selected molecular ion peaks with the same retention time as the metabolites identified in dogs. In humans, these common metabolites represented a similar percentage of the administered dose to that in dogs. The present study demonstrates that NMR, TSP-LC-MS, and FAR-MS are complementary analytical techniques, which allow structural identification of unhydrolyzed drug conjugates. The formation of carbamates of amine-containing drugs may be more common than previously reported.

Drozdzik M, Bialecka M, Mysliwiec K, Honczarenko K, Stankiewicz J, Sych Z. 2003. Polymorphism in the P-glycoprotein drug transporter MDR1 gene: a possible link between environmental and genetic factors in Parkinson's disease. Pharmacogenetics 13(5):259-263.
Abstract: P-glycoprotein is a membrane protein encoded by the MDR1 gene, which demonstrates functional polymorphism. It is present in endothelial cells of the blood-brain barrier, thus limiting accumulation of its substrates in the central nervous system. Many epidemiological studies suggest an association between pesticides, which are substrates for P-glycoprotein, and Parkinson's disease. It was hypothesized that polymorphism of the MDR1 gene could modulate interindividual susceptibility for the disease in subjects exposed to pesticides. In a pilot case-control study involving 107 Parkinson's disease patients (30 early onset and 77 late onset patients; 59 exposed to pesticides and 48 non-exposed) and 103 controls, C3435T polymorphism of the gene was analysed. No statistically significant correlation between MDR1 gene polymorphism and Parkinson's disease was found. The 3435TT genotype was noted more frequently, but not significantly, in patients with early onset compared to late onset disease (23.3% versus 10.4%, respectively). A significant association between patients with parkinsonism exposed to pesticides and C3435T polymorphism of the MDR1 gene was found. Comparing the exposed and non-exposed patients, a statistically higher

frequency of heterozygous subjects was observed (72.9% versus 47.9%, respectively). This genotype was associated with a significant, almost three-fold increased risk of disease. Similarly, a higher frequency of 3435TT subjects was revealed in exposed subjects (15.5%) compared to non-exposed patients (12.5%). In exposed versus non-exposed subjects, patients carrying at least one 3435T allele (i.e. homozygous and heterozygous) had a significant, five-fold higher risk of Parkinson's disease. Thus, it appears that mutation of the MDR1 gene predisposes to damaging effects of pesticides, and possibly other toxic xenobiotics transported by P-glycoprotein, leading to Parkinson's disease.

Du YL, Liu ZG, Chen SD, Lu GQ. 2005 Sep 7. [Effects of different doses of levodopa on paraquat-induced neurotoxicity: an experiment with mice]. Zhonghua Yi Xue Za Zhi 85(34):2400-3.
Abstract: OBJECTIVE: To investigate the effects and mechanisms of different doses of levodopa on paraquat-induced neuro-toxicity. METHODS: 72 C57BL mice were divided into 2 equal groups: acute experiment group and chronic experiment groups. The acute experiment group was re-divided into 2 subgroup: subgroup A to be injected with levodopa of the doses of 0 (distilled water instead), 10 mg/kg, or 100 mg/kg and then paraquat 30 mg/kg (levodopa + paaquat), and then killed 90 minutes after; and subgroup B, to be injected with paraquat 30 mg/kg and then levodopa 0, 10 mg/kg, or 100 mg/kg (paraquat + levodopa), and then killed 2 hours after. The chronic experiment group was re-divided into 2 subgroups to be injected with levodopa + paraquat or paraquat + levodopa once a week for 3 weeks, and then killed 24 hours after the injection. Fluorescent microscopy was used to observe the fluorescent staining of paraquat in the substantia nigra in the acute experiment group and the fluorescent staining of tyrosine hydroxylase (TH) in the substantia nigra in the chronic experiment group. in the chronic experiment group Western blotting was used to examine the protein expression of TH; thioflavine double labeling was used to observe the alpha-synuclein aggregation by immunofluoresence staining and Western blotting. The slices of substantia nigra of the mice in the chronic experiment group treated with distilled water + paraquat were inoculated with or without 250 micromol/L levodopa and then underwent thioflavine staining to observe the alpha-Syn aggregation. RESULTS: The paraquat staining was strongly positive in the substantia nigra of the mice in Group A-1, and was decreased gradually in the group A-2 and A-3. The paraquat staining was strongly positive in the substantia nigra of Group B-1 without a significant difference between Group A-1 and Group B-1, and was not remarkable in Group B-2 and B-3. The TH staining and protein expression in the substantia nigra of Group A-2 were significantly stronger than that of Group A-1 ($P < 0.05$), and the TH staining was remarkably weaker in Group A-3 ($P < 0.05$), as shown by immunofluoresence staining and Western blotting. There was no significant difference in TH staining and protein expression in the substantia nigra among Group A-1, Group B-1, and Group B-2 (all $P > 0.05$). However, the TH staining was remarkably weaker in Group B-3 ($P < 0.05$). The thioflavine and alpha-Syn double staining was significantly weaker in

Groups A-2 and A-3 in comparison with Group A-1. There was no significant difference in the double staining among Group A-1, Group B-1, and Group B-2 (all P > 0.05). However, the double staining was remarkably weaker in Group B-3 (P < 0.05). The thioflavine positive staining in the tissue slices inoculated with levodopa was significantly weaker in comparison with those un-inoculated. CONCLUSION: Pre-treatment with lower dose L-dopa before the paraquat administration is neuroprotective by preventing paraquat from access into central nervous system through a blood-brain barrier competitive uptake mechanism, while higher dose L-dopa shows neurotoxicity through disaggregating alpha-synuclein deposits in Parkinsonian mice.

Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL, Mattson MP. 2002. Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic, neurons in models of Parkinson's disease. J Neurochem 80 (1):101-110.
Abstract: Although the cause of Parkinson's disease (PD) is unknown, data suggest roles for environmental factors that may sensitize dopaminergic neurons to age-related dysfunction and death. Based upon epidemiological data suggesting roles for dietary factors in PD and other age-related neurodegenerative disorders, we tested the hypothesis that dietary folate can modify vulnerability of dopaminergic neurons to dysfunction and death in a mouse model of PD. We report that dietary folate deficiency sensitizes mice to MPTP-induced PD-like pathology and motor dysfunction. Mice on a folate-deficient diet exhibit elevated levels of plasma homocysteine. When infused directly into either the substantia nigra or striatum, homocysteine exacerbates MPTP-induced dopamine depletion, neuronal degeneration and motor dysfunction. Homocysteine exacerbates oxidative stress, mitochondrial dysfunction and apoptosis in human dopaminergic cells exposed to the pesticide rotenone or the pro-oxidant Fe2+. The adverse effects of homocysteine on dopaminergic cells is ameliorated by administration of the antioxidant uric acid and by an inhibitor of poly (ADP-ribose) polymerase. The ability of folate deficiency and elevated homocysteine levels to sensitize dopaminergic neurons to environmental toxins suggests a mechanism whereby dietary folate may influence risk for PD.

Duan WZ, Mattson MP. 1999. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. J Neurosci Res 57 (2):195-206.
Abstract: Parkinson's disease (PD) is an age-related disorder characterized by progressive degeneration of dopaminergic neurons in the substantia nigra (SN) and corresponding motor deficits. Oxidative stress and mitochondrial dysfunction are implicated in the neurodegenerative process in PB, Although dietary restriction (DR) extends lifespan and reduces levels of cellular oxidative stress in several different organ systems, the impact of DR on age-related neurodegenerative disorders is unknown. We report that DR in adult mice results in resistance of dopaminergic neurons in the SN to the toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

MPTP-induced loss of dopaminergic neurons and deficits in motor function were ameliorated in DR rats. To mimic the beneficial effect of DR on dopaminergic neurons, we administered 2-deoxy-D-glucose (2-DG; a nonmetabolizable analogue of glucose) to mice fed ad libitum, Mice receiving 2-DG exhibited reduced damage to dopaminergic neurons in the SN and improved behavioral outcome following MPTP treatment. The 2-DG treatment suppressed oxidative stress, preserved mitochondrial function, and attenuated cell death in cultured dopaminergic cells exposed to the complex I inhibitor rotenone or Fe2+, 2-DG and DR induced expression of the stress proteins heat-shock protein 70 and glucose-regulated protein 78 in dopaminergic cells, suggesting involvement of these cytoprotective proteins in the neuroprotective actions of 2-DG and DR. The striking beneficial effects of DR and 2-DG in models of PD, when considered in light of recent epidemiological data, suggest that DR may prove beneficial in reducing the incidence of PD in humans. J, Neurosci, Res. 57:195-205, 1999, (C) 1999 Wiley-Liss, Inc.

Duan WZ, Zhang ZM, Gash DM, Mattson MP. 1999. Participation of prostate apoptosis response-4 in degeneration of dopaminergic neurons in models of Parkinson's disease. Ann Neurol 46(4):587-597.
Abstract: Dysfunction and death of midbrain dopaminergic neurons underlies the clinical features of Parkinson's disease (PD). Increasing evidence suggests roles for oxidative stress and a form of cell death called apoptosis in the pathogenesis of PD. Me recently identified a 38-kd protein called prostate apoptosis response-4 (Par-4), which is rapidly induced in cultured neurons after exposure to apoptotic insults, and appears to play a necessary role in the cell death process. We now report that Par-4 levels increase dramatically in midbrain dopaminergic neurons of monkeys and mice exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The increase in Par-4 levels occurs in both neuronal cell bodies in the substantia nigra and their axon terminals in the striatum, and precedes loss of tyrosine hydroxylase immunoreactivity and cell death. In the monkey model, Par-4 levels were also increased in several brain regions (red nucleus, lateral geniculate nucleus, and cerebral cortex) in which functional alterations have previously been documented in PD patients and MPTP-treated monkeys. Exposure of cultured human dopaminergic neural cells to the complex I inhibitor rotenone, or to Fe2+, resulted in Par-4 induction, mitochondrial dysfunction, and subsequent apoptosis. Blockade of Par-4 induction by antisense treatment prevented rotenone- and Fe2+-induced mitochondrial dysfunction and apoptosis demonstrating a critical role for Par-4 in the cell death process. The data suggest that Par-4 may be involved in the neurodegenerative process in PD.

Dukes AA, Korwek KM, Hastings TG. 2005. The effect of endogenous dopamine in rotenone-induced toxicity in PC12 cells. Antioxidants & Redox Signaling 7 (5-6):630-638.
Abstract: Deficiencies in Complex I have been observed in Parkinson's disease (PD) patients. Systemic exposure to rotenone, a Complex I inhibitor, has been shown to lead to selective dopaminergic cell death in vivo and toxicity in many in vitro models, including dopaminergic cell

cultures. However, it remains unclear why rotenone seems to affect dopaminergic cells more adversely. Therefore, the role of dopamine (DA) in rotenone-induced PC12 cell toxicity was examined. Rotenone (1.0 mu M) caused significant toxicity in differentiated PC12 cells, which was accompanied by decreases in ATP levels, changes in catechol levels, and increased DA oxidation. To determine whether endogenous DA makes PC12 cells more susceptible to rotenone, cells were treated with the tyrosine hydroxylase inhibitor a-methyl-p-tyrosine (AMPT) to reduce DA levels prior to rotenone exposure, and then cell viability was measured. No changes in rotenone-induced toxicity were observed with or without AMPT treatment. However, a potentiation of toxicity was observed following coexposure of PC12 cells to rotenone and methamphetamine. To determine whether this effect was due to DA, PC12 cells were depleted of DA prior to methamphetamine and rotenone cotreatment, resulting in a large attenuation in toxicity. These findings suggest that DA plays a role in rotenone-induced toxicity and possibly the vulnerability of DA neurons in PD.

Duzcan F, Zencir M, Ozdemir F, Cetin GO, Bagci H, Heutink P, Bonifati V, Sahiner T. 2003. Familial influence on parkinsonism in a rural area of Turkey (Kizilcaboluk-Denizli): A community-based case-control study. Mov Disord 18(7):799-804.
Abstract: This population-based study on parkinsonism in a genetically isolated community from a rural area of Turkey aimed to provide a selective evaluation of environmental and heritable risk factors. An increased prevalence of parkinsonism (4.1%) was detected in the village of Kizilcaboluk for people 65 years of age and older. This study included 36 patients with parkinsonism living in Kizilcaboluk and three times that number of age- and sex-matched people serving as controls. A questionnaire including demographic data, family history, education, occupation, data on exposures to pesticides, smoking, alcohol intake, and head trauma was administered. We found a significant association of parkinsonism cases with a positive family history in first-degree relatives (odds ratio [OR], 7.48; 95% confidence interval [CI], 2.52-22.17; P < 0.0001) and with pesticide exposure (OR, 2.96; 95% CI, 1.31-6.69; P = 0.015) compared to the control subjects. The value of genetically isolated populations for the identification of genetic risk factors for common and complex disorders has gained much attention recently because the genetic make-up of these populations is likely to be less complex than that of the general population and our findings should prompt investigations to the nature of a familial aggregation of parkinsonism in this population. (C) 2003 Movement Disorder Society.

Ebadi M, Kumari MVR, Hiramatsu M, Hao R, Pfeiffer RF, Rojas P. 1998. Metallothionein, neurotrophins and selegiline in providing neuroprotection in Parkinson's disease. Restorative Neurology and Neuroscience 12(2-3): 103-111.
Abstract: The finding that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) elicits parkinsonism in human beings suggests that endogenous or xenobiotic neurotoxic compounds may be involved in the etiology of

Parkinson's disease (PD). We have shown that cerebrospinal fluid (CSF) of newly diagnosed and drug untreated patients with PD contains a low molecular weight substance(s) which inhibits the growth and function of dopaminergic neurons in culture. In addition, selegiline in a dosage below the level that inhibits monoamine oxidase B (MAO-B), protects dopaminergic neurons in culture against toxic factor(s) present in the CSF of patients with PD, and the said effect is mediated via elaboration of brain-derived neurotrophic factor (BDNF). In view of the fact that 6-hydroxydopamine (6-OHDA) or MPTP causes parkinsonism by generating free radicals, and inducers of metallothionein (MT) isoforms avert the said neurotoxicity, we intended to learn whether MT isoforms were capable of scavenging free radicals. By employing electron spin resonance spectroscopy (ESR), we examined for the first time the free radical scavenging effects of MT-I and MT-II isoforms on four types of free radicals. Solutions of 0.15 mM of MT-I and 0.3 mM of MT-II scavenged the 1,1-diphenyl-2-picryrhydrazyl radicals completely. Furthermore, they were able to scavenge hydroxyl radicals generated in a Fenton reaction. Moreover, MT-I scavenged almost 90 % of the superoxide generated by the hypoxanthine and xanthine oxidase system, while MT-II could only scavenge 40 %. By using 2,2,6,6-tetramethyl-4-piperidone as a "spin-trap" for the reactive oxygen species (containing singlet oxygen, superoxide and hydroxyl radicals) generated by photosensitized oxidation of riboflavin, and measuring the relative signal intensities of the resulting stable nitroxide adduct, 2,2,6,6-tetramethyl-4-piperidone- 1-oxyl, we observed that MT-II could scavenge 92 %, while MT-I could completely scavenge all the reactive species generated. The results of this investigation are interpreted to suggest that selegiline by preventing the generation of free radicals, MT isoforms by scavenging free radicals, and neurotrophins by rescuing dopaminergic neurons are capable of attenuating oxidative stress and of providing neuroprotection in PD.

Ebadi M, Sharma SK, Wanpen S, Amornpan A. 2004. Coenzyme Q(10) inhibits mitochondrial complex-1 down-regulation and nuclear factor-kappa B activation. Journal of Cellular and Molecular Medicine 8(2):213-222. Abstract: We have used control-homozygous weaver mutant, and -heterozygous weaver mutant mice in order to explore the basic molecular mechanism of neurodegeneration and the neuroprotective potential of coenzyme Q(10). Homozygous weaver mutant mice exhibited progressive neurodegeneration in the hippocampus, striatum, and cerebellum, and a reduction in the striatal levels of dopamine and coenzyme Qs (Q(9) and Q (10)) without any significant changes in norepinephrine and serotonin. Mitochondrial complex-1 was down regulated; whereas nuclear factor-kappa B was up regulated in homozygous weaver mutant mice. Rotenone inhibited complex-1, enhanced nuclear factor-kappa B, and caused apoptosis in human dopaminergic (SK-N-SH) neurons; whereas nuclear factor-kappa B antibody suppressed rotenone-induced apoptosis, suggesting that enhancing coenzyme Q(10) synthesis and suppressing the induction of NF-kappa B, may provide neuroprotection.

Eichelbaum M, Kroemer HK, Mikus G. 1992. Genetically-determined differences in

drug-metabolism as a risk factor in drug toxicity. Toxicol Lett 64-5(Sp. Iss. Si):115-122.
Abstract: Drug metabolizing, enzymes are of paramount importance in drug detoxification as well as chemical mutagenesis, carcinogenesis and toxicity via metabolic activation. Thus genetically determined differences in the activity of these enzymes can influence individual susceptibility to adverse drug reactions, drug induced diseases and certain types of chemically induced cancers. The genetic polymorphisms of three human drug metabolizing enzymes, namely N-acetyltransferase and two cytochrome P-450 isozymes (P-4502D6: debrisoquine/sparteine polymorphism, P4502C8-10: mephenytoin polymorphism) have been firmly established. Based on the metabolic handling of certain probe drugs, the population can be divided into two phenotypes- the rapid acetylator/ extensive metabolizer and slow acetylator/poor metabolizer. These polymorphisms have provided useful tools to study the relationship between genetically determined differences in the activity of drug metabolizing enzymes and the risk for adverse drug reactions and certain types of chemically-induced diseases and cancers. With regard to the susceptibility of the two phenotypes, drug mediated toxicity for the following scenarios can be anticipated. (1) The toxicity of the drug is caused by the parent compound and the elimination of the drug proceeds exclusively via the polymorphic enzyme. No alternate pathways of biotransformation are available. Thus the slow acetylator/poor metabolizer phenotype will be more prone to such a type of toxicity since, at the same level of exposure, this phenotype will accumulate the drug as a result of impaired metabolism (e.g. isoniazid polyneuropathy, perhexiline polyneuropathy, pesticide induced Parkinsons disease). (2) The polymorphic pathway is a major route of detoxification. Impairment of this pathway shifts the metabolism to an alternate pathway via which a reactive intermediate is being formed. In such a situation the slow acetylator/poor metabolizer phenotype constitutes a major risk factor for toxicity (eg. isoniazid hepatotoxicity). (3) The toxicity is mediated by a reactive intermediate generated by a polymorphic enzyme. Hence extensive metabolizers are at a much higher risk than poor metabolizers to develop toxicity or cancer (e.g. bronchial carcinoma in smokers, not chemically induced aggressive bladder cancer).

Elbaz A, Levecque C, Clavel J, Vidal JS, Richard F, Amouyel P, Alperovitch A, Chartier-Harlin MC, Tzourio C. 2004. CYP2D6 polymorphism, pesticide exposure, and Parkinson's disease. Ann Neurol 55(3):430-434.
Abstract: We performed a case-control study of Parkinson's disease (PD) in a population characterized by a high prevalence of pesticide exposure and studied the joint effect of pesticide exposure and CYP2D6. Although they are based on a small group of subjects with the joint exposure, our findings are consistent with a gene-environment interaction disease model according to which (1) pesticides have a modest effect in subjects who are not CYP2D6 poor metabolizers, (2) pesticides' effect is increased in poor metabolizers (approximately twofold), and (3) poor metabolizers are not at increased PD risk in the absence of pesticide exposure.

Elbaz A, Levecque C, Clavel J, Vidal JS, Richard F, Correze JR, Delemotte B, Amouyel P, Alperovitch A, Chartier-Harlin MC, Tzourio C. 2003. S18Y polymorphism in the UCH-L1 gene and Parkinson's disease: Evidence for an age-dependent relationship. Mov Disord 18(2):130-137.
Abstract: We studied the relationship between Parkinson's disease (PD) and the S18Y polymorphism in the UCH-L1 gene and the effect on this relationship of age at onset, smoking, and pesticides. Patients requested free health coverage for PD to the Mutualite Sociale Agricole (MSA), the French health insurance organization for people whose work is related to agriculture. Controls requested reimbursement of health expenses to the MSA. A maximum of three controls were matched to each case. Analyses included participants with both parents born in Europe. There were no differences in S18Y genotypes between patients (n = 209; 67% SS, 32% SY, 1% YY) and controls (n = 488; 66% SS, 30% SY, 4% YY). The relationship between PD and S18Y was modified by age at onset (P=0.03). The Y allele was inversely associated with PD for patients with onset before 61 years (odds ratio [OR] = 0.53; 95% confidence interval [CI], 0.29-0.99); there was no association for older patients (62-68 years: OR = 1.21; 95% CI, 0.67-2.20; >68 years: OR = 1.24; 95% CI, 0.67-2.31). Among patients, Y carriers had a later onset than noncarriers (P = 0.04). These findings were not modified or confounded by smoking and pesticides. In this community-based case-control study, carriers of the Y allele were at decreased risk of developing PD at a young age, independently of pesticides and smoking. (C) 2002 Movement Disorder Society.

Elwan MA, Richardson JR, Guillot TS, Caudle WM, Miller GW. 2005 Jul 7. Pyrethroid pesticide-induced alterations in dopamine transporter function. Toxicol Appl Pharmacol .
Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease affecting the nigrostriatal dopaminergic pathway. Several epidemiological studies have demonstrated an association between pesticide exposure and the incidence of PD. Studies from our laboratory and others have demonstrated that certain pesticides increase levels of the dopamine transporter (DAT), an integral component of dopaminergic neurotransmission and a gateway for dopaminergic neurotoxins. Here, we report that repeated exposure (3 injections over 2 weeks) of mice to two commonly used pyrethroid pesticides, deltamethrin (3 mg/kg) and permethrin (0.8 mg/kg), increases DAT-mediated dopamine uptake by 31 and 28%, respectively. Using cells stably expressing DAT, we determined that exposure (10 min) to deltamethrin and permethrin (1 nM-100 muM) had no effect on DAT-mediated dopamine uptake. Extending exposures to both pesticides for 30 min (10 muM) or 24 h (1, 5, and 10 muM) resulted in significant decrease in dopamine uptake. This reduction was not the result of competitive inhibition, loss of DAT protein, or cytotoxicity. However, there was an increase in DNA fragmentation, an index of apoptosis, in cells exhibiting reduced uptake at 30 min and 24 h. These data suggest that up-regulation of DAT by in vivo pyrethroid exposure is an indirect effect and that longer-term exposure of cells results in apoptosis. Since DAT can

greatly affect the vulnerability of dopamine neurons to neurotoxicants, up-regulation of DAT by deltamethrin and permethrin may increase the susceptibility of dopamine neurons to toxic insult, which may provide insight into the association between pesticide exposure and PD.

Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT, Scott KC, Hudnell K, Anger WK, Camicioli R. 2001. Parkinsonism and occupational exposure to pesticides. Occup Environ Med 58(9):582-589.
Abstract: Objective-To examine the risk of parkinsonism related to lifetime occupational exposure to pesticides among a cohort of men, mostly orchardists, in Washington State. Methods-All 310 subjects in this study had previously participated in a cohort study of men occupationally exposed to pesticides. Subjects were given a structured neurological examination and completed a self administered questionnaire which elicited detailed information on pesticide (insecticide, herbicide, and fungicide) use throughout their working careers. Demographic characteristics were also sought. Subjects had a mean age of 69.6 years (range 49-96, SD 8.1). There were 238 (76.8%) subjects who reported some occupational exposure to pesticides, whereas 72 (23.2%) reported none. Parkinsonism was defined by the presence of two or more of rest tremor, rigidity, bradykinesia, and impairment of postural reflexes in subjects not on antiparkinsonian medication, or the presence of at least one sign if they were on such medication. Parkinson's disease was not studied explicitly because of the difficulty in distinguishing it from other parkinsonian syndromes. A generalised linear model was used to estimate prevalence ratios (PRs) for parkinsonism relative to history of farming, pesticide use, and use of well water. Results-A PR of 2.0 (95% confidence interval (95% CI) 1.0 to 4.2) was found for subjects in the highest tertile of years of exposure to pesticides; a similarly increased, non-significant, PR was found for the middle tertile (1.9 (95% CI 0.9 to 4.0)), although a trend test did not show a significant exposure-response relation. No increased risks were found associated with specific pesticides or pesticide classes, nor with a history of farming or use of well water. Conclusion-Parkinsonism may be associated with long term occupational exposure to pesticides, although no associations with specific pesticides could be detected. This finding is consistent with most of the publications on this topic.

Fall PA, Fredrikson M, Axelson O, Granerus AK. 1999. Nutritional and occupational factors influencing the risk of Parkinson's disease: A case-control study in southeastern Sweden. Mov Disord 14(1):28-37.
Abstract: PURPOSE AND METHODS: To investigate the possible impact of nutritional and environmental risk factors for idiopathic Parkinson's disease (IP), a case-control study was performed in the county of Ostergotland in southeastern Sweden. The study involved 113 cases of IP and 263 control subjects. Dietary, drinking, and smoking habits, as well as previous occupation, were requested in a structured questionnaire. RESULTS: No increased risk was found for any of the nutritional items in which information was requested. A reduced risk was found for coffee, wine, and liquor at various consumption levels but also for fried or broiled meat, smoked ham or meat, eggs, French loaf or white bread, and tomatoes. All

these food and drink items contain niacin. As in many studies, the frequency of preceding and present smoking was reduced in IP patients. Various occupational groups and exposures were analyzed and increased risks of TP in men were found for agricultural work along with pesticide exposure; this was also the case for male carpenters and female cleaners. CONCLUSIONS: The findings indicate that nutritional factors and occupational exposures, especially to pesticides, could be of etiologic importance in IP.

Farlow MR. 2003. Update on rivastigmine. Neurologist 9(5):230-234.
Abstract: Background: Rivastigmine is a carbamate drug designed to inhibit both acetylcholinesterase and butyrylcholinesterase by reversibly covalently bonding to these enzymes. Butyrylcholinesterase increases as Alzheimer disease progresses, so its inhibition may become more important as the disease worsens. Metabolism of rivastigmine occurs at the synapse rather than at the liver and previous studies have demonstrated no drug-drug interactions. Rivastigmine has a half-life at the synapse of 9 hours allowing for bid dosing. Review Summary: Effective therapy requires up-titration from initial dosage of 3 mg/d to 6 mg/d with additional increases to 9 mg or 12 mg/d giving additional benefits in some patients. Beneficial effects with rivastigmine therapy in the functioning of activities of daily living, behavior, cognition, and global functioning have been demonstrated in patients with mild to moderate Alzheimer disease in 4 large double-blind, placebo-controlled multicenter clinical trials. Potential adverse effects of nausea, vomiting, or diarrhea in these original Alzheimer trials with rapid (every week) dosage increases occurred in up to 34% of patients and can be minimized by slower monthly up-titrations. Rivastigmine also was proven effective in decreasing psychiatric symptoms and cognitive deficits in a large double-blind, placebo-controlled trial in patients with diffuse Lewy body disease. Other studies have suggested that rivastigmine improves symptoms in nursing home patients with more severe stage Alzheimer disease, Parkinson dementia, and subcortical dementia. Follow-up studies have suggested that rivastigmine may delay disease progression and, in patients discontinuing the drug, no withdrawal effects were seen. Conclusion: Rivastigmine is an effective therapeutic, agent for treating cognitive and behavioral symptoms in Alzheimer disease and diffuse Lewy body disease and may also have beneficial effects in vascular and Parkinson dementias.

Feger J, Pessigliore M, Francois C, Tremblay L, Hirsch E. 2002 Jan. [Experimental models of Parkinson's disease]. Ann Pharm Fr 60(1):3-21.
Abstract: Parkinson's disease is a neurodegenerative condition who is related to a large loss of nigral dopaminergic neurons leading to a depletion of dopamine in the striatum. Experimental research is required in order to increase our knowledge on the cellular mechanism and functional consequences of this degenerative process. These models allow investigations of new therapeutics in order to improve the treatment of patients or to test new drugs able to protect any remaining dopaminergic neurons. It is relatively easy to obtain animal models of this disease since the target structure and the neuronal population are clearly defined. Two

neurotoxic compounds are available for inducing animal models of Parkinson's disease, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). A new one, rotenone, requires further investigations. Each of the neurotoxic compounds requires a specific protocol which can be used either with rodents or non-human primates. Progressive lesioning, using MPTP on green african monkeys (Cercopithecus aethiops sabaeus) provides the most reliable model of the idiopathic disease.

Feldman JM, Feldman MD. 1990. Sequelae of attempted suicide by cyanide ingestion: a case report. Int J Psychiatry Med 20(2):173-9.
Abstract: A twenty-eight-year-old man presented emergently after ingesting 800 mg of potassium cyanide in a suicide attempt. He survived only with intensive medical and psychiatric intervention, and went on to develop severe parkinsonian symptoms, including profound micrographia and hypersalivation. Bilateral, symmetrical basal ganglial abnormalities were demonstrated with magnetic resonance imaging. Survival following cyanide poisoning is rare; the clinical, radiologic, and neuropathologic sequelae in other documented cases are reviewed.

Fern R. 2003. Variations in spare electron transport chain capacity: The answer to an old riddle? J Neurosci Res 71(6):759-762.
Abstract: Several neurological diseases involve focal injury of specific brain structures. Poisons of the electron transport chain complexes (ETCC) can also produce selective injury of brain structures when given systemically and have been implicated in the development of neurological disease. Why ETCC poisons damage particular brain regions is unclear. Calculations of the relative ETCC expression level to glucose utilization rate (GUR) ratio from published observations here reveal that a low ETCC/GUR ratio predisposes a brain structure to injury by a poison of that complex. While GUR can rise with increased neuronal activity, ETCC expression is fixed in the short term. A high ETCC/GUR therefore represents surplus ETCC capacity, allowing for increased ATP generation with short-term increases in demand. A low ETCC/GUR indicates the opposite and will lead to energy failure when the specific ETCC is poisoned. These observations may explain why cyanide, a specific ETCC (IV) inhibitor, can produce selective injury of white matter, which has the lowest ETCC (IV)/GUR found in the brain. They are also consistent with the selective damage of the striatum produced by poisons such as rotenone, a form of injury implicated in Parkinson's disease. The striatum has a low ETCC (I)/GUR ratio, whereas rotenone is a selective ETCC (I) inhibitor. (C) 2003 Wiley-Liss, Inc.

Fernandez C, Nieto O, Fontenla JA, Rivas E, De Ceballos ML, Fernandez-Mayoralas A. 2003. Synthesis of glycosyl derivatives as dopamine prodrugs: interaction with glucose carrier GLUT-1. Organic & Biomolecular Chemistry 1(5):767-771.
Abstract: Glucosyl dopamine (DA) derivatives may represent a new class of DA prodrugs that would interact with glucose transporter GLUT-1, present in the blood-brain barrier, and generate DA in the brain. Therefore,

compounds bearing the sugar moiety linked to either the amino group or the catechol ring of DA through amide, ester, carbamate, peptide or glycosidic bonds were synthesized. The behavior of the compounds as prodrugs was monitored in different media and the affinity of the glycoconjugates for the glucose carrier GLUT-1 using human erythrocytes was also studied. Most of the compounds were markedly stable in buffer and plasma, and several compounds released DA when incubated with brain extracts and the rate was related to the bond linking DA with glucose. The new glucosyl conjugates substituted at the C-6 position of the sugar were more potent inhibitors of glucose transport when compared to C-1 and C-3 substituted derivatives. This work provides structure-activity information about the interaction of substituted glucose with the GLUT-1 transporter.

Ferrante RJ, Schulz JB, Kowall NW, Beal MF. 1997. Systemic administration of rotenone produces selective damage in the striatum and globus pallidus, but not in the substantia nigra. Brain Res 753(1):157-162.
Abstract: Complex I dysfunction has been implicated in the pathogenesis of Parkinson's disease and in the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which produces a Parkinsonian syndrome in experimental animals and humans. Rotenone is an insecticide which is a specific inhibitor of complex I. We examined the pattern of central nervous system damage produced by i.v. systemic administration of rotenone in rats. Rotenone produced selective damage in the striatum and the globus pallidus, but the substantia nigra was spared. These results are consistent with prior reports suggesting that the selective vulnerability of the substantia nigra to MPTP involves both uptake by the dopamine transporter as well as complex I inhibition, and they show that rotenone produces a unique pattern of central nervous system damage. (C) 1997 Elsevier Science B.V.

Ferraz HB, Bertolucci PH, Pereira JS, Lima JG, Andrade LA. 1988 Apr. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. Neurology 38(4):550-3.
Abstract: Manganese (Mn) poisoning, a well-known hazard in miners and industrial workers, shares many features with Parkinson's disease. Two young agricultural workers with a parkinsonian syndrome, who mentioned exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate), led us to investigate a new possible source of Mn intoxication. Fifty male rural workers with occupational exposure to maneb were compared with 19 rural workers without fungicide exposure. We noted significantly higher prevalence of plastic rigidity with cogwheel phenomenon, headache, fatigue, nervousness, memory complaints, and sleepiness in the exposed group. In addition, we saw other neurologic signs, such as postural tremor, cerebellar signs, and bradykinesia, although without statistical significance. The data suggest that occupational exposure to pesticides containing Mn is a possible source of Mn intoxication of the CNS.

Firestone JA, Franklin GM, Longstreth WT, Smith-Weller T, Swanson PD,

Checkoway H. 2002. Residential pesticide exposure and risk of Parkinson's disease. Epidemiology 13(4 ):S222.

Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Checkoway H. 2005. Pesticides and risk of Parkinson disease a population-based case-control study. Arch Neurol 62(1):91-95.
Abstract: Background: Pesticide exposures are suspected risk factors for Parkinson disease (PD), but epidemiological A servations have been inconsistent. Objective: To investigate associations between pesticide exposures and idiopathic PD. Design: Population-based case-control study. Setting: Group Health Cooperative, a health care system in western Washington State, and the University of Washington. Participants: Two hundred fifty incident PD case patients and 388 health), control subjects (age- and sex-matched). We assessed self-reported pesticide exposures using a structured inter-view. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using logistic regression models, controlling for age, sex, and smoking. Results: Odds ratios for occupational exposures were not significant but suggested a gradient that paralleled occupational exposures (pesticide worker OR, 2.07: 95% CI: 0.67-6.38; cropfanner: OR., 1.65; 95% CI, 0 84 -3.27; animal and crop farmer. OR, 1.10; 95% CI, 0.60-2.00; and dairy farmer: OR, 0.88; 95% CI, 0.46-1.70). Odds ratios for organophosphates paralleled the World Health Organization hazard classifications. with parathion much higher than diazinon or malathion. We also found elevated ORs from herbicides (OR, 1.41; 95% CI, 0.51-3.88) and paraquat (OR, 1.67; 95% CI, 0.22-12-76). We found no evidence of risk from home-based pesticide exposures. We found significantly increased ORs from life-long well water consumption (OR, 1.81; 95% CI, 1.02-3.21). Conclusions: The findings for occupational pesticide exposures are consistent with a growing body of information linking pesticide exposures with PD. However, the lack of significant associations. absence of associations with home-based exposures, and weak associations with rural exposures suggest that pesticides did not play a substantial etiologic role in this population. 0

Fiskum G, Starkov A, Polster BM, Chinopoulos C. 2003. Mitochondrial Mechanisms of Neural Cell Death and Neuroprotective Interventions in Parkinson's DiseaseVolume 991. p 111-119. Parkinson's Disease: the Life Cycle of the Dopamine Neuron: Annals of the New York Academy of Sciences.
Abstract: Mitochondrial dysfunction, due to either environmental or genetic factors, can result in excessive production of reactive oxygen species, triggering the apoptotic death of dopaminergic cells in Parkinson's disease. Mitochondrial free radical production is promoted by the inhibition of electron transport at any point distal to the sites of superoxide production. Neurotoxins that induce parkinsonian neuropathology, such as MPP+ and rotenone, stimulate superoxide production at complex I of the electron transport chain and also stimulate free radical production at proximal redox sites including mitochondrial matrix dehydrogenases. The oxidative stress caused by elevated mitochondrial production of reactive oxygen species promotes the expression and (or) intracellular distribution of the proapoptotic protein Bax to the mitochondrial outer membrane.

Interactions between Bax and BH3 death domain proteins such as tBid result in Bax membrane integration, oligomerization, and permeabilization of the outer membrane to intermembrane proteins such as cytochrome c. Once released into the cytosol, cytochrome c together with other proteins activates the caspase cascade of protease activities that mediate the biochemical and morphological alterations characteristic of apoptosis. In addition, loss of mitochondrial cytochrome c stimulates mitochondrial free radical production, further promoting cell death pathways. Excessive mitochondrial Ca2+ accumulation can also release cytochrome c and promote superoxide production through a mechanism distinctly different from that of Bax. Ca2+ activates a mitochondrial inner membrane permeability transition causing osmotic swelling, rupture of the outer membrane, and complete loss of mitochondrial structural and functional integrity. While amphiphilic cations, such as dibucaine and propranolol, inhibit Bax-mediated, cytochrome c release, transient receptor potential channel inhibitors inhibit mitochondrial swelling and cytochrome c release induced by the inner membrane permeability transition. These advances in the knowledge of mitochondrial cell death mechanisms and their inhibitors may lead to neuroprotective interventions applicable to Parkinson's disease.

Fitsanakis VA, Amarnath V, Moore JT, Montine KS, Zhang J, Montine TJ. 2002. Catalysis of catechol oxidation by metal-dithiocarbamate complexes in pesticides. Free Radic Biol Med 33(12):1714-1723.
Abstract: Dithiocarbamate (DTC)-based pesticides have been implicated in Parkinson's disease (PD) through epidemiological links to increased risk of PD, clinical reports of parkinsonism following occupational exposure to the DTC-based pesticide maneb, and experimental studies showing dopaminergic neurodegeneration with combined exposure of rats to maneb and paraquat. We hypothesize that the manganese-ethylene-bis-dithiocarbamate (MnEBDC) complex in maneb may produce oxidative stress by catalyzing catechol oxidation. We tested this hypothesis by performing a structure-function analysis of metal-EBDC and metal-diethyldithiocarbamate (DEDC) complexes of Mn2+, Zn2+, and Cu2+ to catalyze oxidation of N-acetyldopamine (NA-DA) and 3,4-dihydroxyphenyl acetic acid (DP) in the presence and absence of N-acetylcysteine (NAC), a model of glutathione. Both Mn-DTCs retained the capacity of the parent ion to catalyze one-electron oxidation of NA-DA, but lost the ability to catalyze DP oxidation. Strikingly, while Zn2+ did not catalyze catechol oxidation, both Zn-DTCs catalyzed one-electron oxidation of NA-DA but not DP. While Cu2+ catalyzed oxidation of both catechols, Cu-DTCs were inert. Similar results were obtained with MnEBDC and dopamine or norepinephrine; however, zinc-ethylene-bis-dithiocarbamate was less efficient at catalyzing oxidation of these catechols. Our results point to the potential for manganese- and zinc-containing EBDC pesticides to promote oxidative stress in catecholaminergic regions of the brain. (C) 2002 Elsevier Science Inc.

Fleming L, Mann JB, Bean J, Briggle T, Sanchezramos JR. 1994. Parkinsons-disease and brain levels of organochlorine pesticides. Ann Neurol 36(1):

100-103.
Abstract: Epidemiological studies have suggested an etiologic relationship between pesticide exposure and Parkinson's disease (PD). Organochlorine pesticides were assayed in postmortem brain samples from 20 PD, 7 Alzheimer's disease (AD), and 14 nonneurological control cases. The three groups were similar in age at death, sex, and demographic variables. Only two of 16 pesticide residues screened were detected. A long-lasting residue of DDT (pp-DDE) was found in the majority of cases of PD and AD, as well as in all the control cases; pp-DDT was significantly more likely to be found in AD controls than the PD cases (Fisher's exact two-tailed, P = 0.04). Dieldrin was detected in 6 of 20 PD brains, 1 of 7 AD, and in none of 14 control samples. Despite the relatively small number of brains assayed, the association between Dieldrin and the diagnosis of PD was highly significant (P = 0.03). Dieldrin, a lipid-soluble, long-lasting mitochondrial poison, should be investigated as a potential etiological agent of Parkinsonism.

Fleming LE, Herzstein JA. 1997. Emerging issues in pesticide health studies. Occupational Medicine-State of the Art Reviews 12(2):387-397.

Fleming SM, Zhu CN, Fernagut PO, Mehta A, Dicarlo CD, Seaman RL, Chesselet MF. 2004. Behavioral and immunohistochemical effects of chronic intravenous and subcutaneous infusions of varying doses of rotenone. Exp Neurol 187(2):418-429.
Abstract: Mitochondrial toxins such as the complex 1 inhibitor rotenone are widely used as pesticides and may be present in military environments. Administration of rotenone can induce biochemical and histological alterations similar to those of Parkinson's disease in rats. However, only a subset of animals show these effects and it is unclear whether more subtle alterations are caused by chronic administration of rotenone in those animals that appear resistant to its toxic effects on dopaminergic nerve terminals. To address this question, vehicle or rotenone (2.0, 2.5, or 3.5 mg/kg/day) was administered intravenously or subcutaneously for 21 days to adult rats, and rotenone effects on survival, motor behavior, and striatal tyrosine hydroxylase immunoreactivity (TH-IR) were examined. Both intravenous and subcutaneous rotenone induced a dose-dependent decrease in survival rates. Surviving animals showed a decrease in spontaneous rearing. Locomotor activity and movement initiation time were also altered in some of the experimental groups. Confirming previous results, TH-IR in the striatum was markedly decreased in rats that fell ill early in the study and in a few of the surviving rats with high rotenone doses. However, none of the surviving rats receiving 2.0 mg/kg/day showed TH-IR loss reminiscent of Parkinson's disease, and loss of striatal TH-IR across doses was not correlated with motor behavior in individual rats. Thus, chronic administration of low doses of rotenone induces motor anomalies even in animals that do not develop histological signs of Parkinson's disease, indicating a pervasive neurological effect of moderate mitochondrial dysfunction in vivo. (C) 2004 Elsevier Inc. All rights reserved.

Fogliani J, Giraud E, Henriquet D, Maitrasse B. 1993. [Voluntary barium

poisoning]. Ann Fr Anesth Reanim 12(5):508-11.
Abstract: A 45-year-old man attempted to commit suicide by ingesting a large amount of barium. In some hours, he experienced generalized muscle weakness with hypokalaemia, treated by large dose of potassium (440 mmol in the first day). This weakness resulted in difficulties in swallowing and respiratory failure requiring mechanical ventilation. An anuric renal insufficiency started early, requiring haemodialysis for three weeks. It was induced probably by renal toxicity of barium and recovered completely. Later, the patient experienced an extrapyramidal syndrome initiated by tremor and myoclonia. Hypertonia induced a parkinsonian rheumatism, fixing the two hands in an irreducible position. There was also a contracture of superior sphincter of oesophagus, with severe disturbance of deglutition, ending after three months only. MRI study showed a bilateral hypersignal in basal ganglia and thalamus. It remains unknown whether this neurological syndrome was toxic or ischaemic. This patient remained under mechanical ventilation for three months because of disturbances of deglutition. He was discharged to his home at the 6th month. One year later he was still adynamic, but able to carry our rather precise movements.

Fonck C, Baudry M. 2003. Rapid reduction of ATP synthesis and lack of free radical formation by MPP+ in rat brain synaptosomes and mitochondria. Brain Res 975(1-2):214-221.
Abstract: MPTP is a neurotoxin thought to damage dopaminergic neurons through free radical formation. MPTP is metabolized in the brain to MPP+, which is taken up into dopaminergic neurons via the doparnme transporter and assumed to impair mitochondrial function. We used striatal synaptosomes and telencephalic mitochondria to further investigate MPP+ mechanism of action. For comparison, the respiratory toxins FCCP, a cyanide analog that uncouples mitochondrial ATP production, and rotenone, a NADH dehydrogenase inhibitor, were also tested. FCCP, MPP+ and rotenone caused a rapid but stable decrease in [H-3]dopamine (DA) uptake by striatal synaptosomes. Two free radical scavengers, the salen-manganese complex EUK-134, and the spin trap s-PBN, did not prevent MPP+-induced decrease in DA uptake. However, addition of ATP during synaptosome preparation resulted in partial recovery of MPP+-induced [H-3]DA uptake decrease. Generation of oxygen free radicals by treatment of telencephalic mitochondria with MPP+, FCCP, or rotenone, was evaluated by measuring DCF fluorescence, while light emission by the luciferin-luciferase complex was used to determine ATP levels. MPP+, unlike rotenone, did not produce oxygen free radicals, but rather blocked ATP production in mitochondria, as did FCCP and rotenone. Taken together, these results suggest that MPP+ toxicity, at least during its initial stages, is primarily due to a decrease in ATP synthesis by mitochondria and not to free radical formation. (C) 2003 Elsevier Science B.V. All rights reserved.

Fong CS, Chen CW, Wu RM. 2005. Pesticides exposure and genetic polymorphism of paraoxonase in the susceptibility of Parkinson's disease. Mov Disord 20:S88.

Fong CS, Cheng CW, Wu RM. 2005 Jun. Pesticides exposure and genetic polymorphism of paraoxonase in the susceptibility of Parkinson's disease. Acta Neurol Taiwan 14(2):55-60.
Abstract: PURPOSE: The manifestation of Parkinson's disease (PD) is characterized by bradykinesia, resting tremor, and rigidity. The etiology of PD remains unknown. Recently several studies suggest that some environmental and genetic factors may be related to the cause of PD. Genetic variation in xenobiotic metabolizing enzymes involved in the disposition of pesticides, such as paraoxonase I (PON 1), may increase the risk of PD. We investigated the association between PON1 polymorphism, pesticides exposure and risk of Parkinson's disease in Taiwanese population. METHODS: We enrolled 162 controls and 125 patients with idiopathic PD. Histories of exposures to environmental factors and other information were collected with a questionnaire filled out during a face-to-face interview with the subject. The data included years of farming, drinking water sources, occupational exposures to pesticides, duration and the initial age of the pesticides exposure. Buccal mucosa cells are collected from each subject and PON1 polymorphism at codon 54 (L and M alleles) is studied with PCR-based restriction fragment length polymorphism (RFLP) analysis. RESULTS: There is significant association between the risk of PD and exposure to pesticides (OR=1.72, 95% CI=1.07-2.75). On the otherhand, no significant differences are found in PON1 genotype or allelic distribution between PD and control groups. We further investigated participants who had reported exposure to pesticides and found that the frequency distribution of PON1 genotypes did not differ significantly between patients and controls. CONCLUSION: The present survey reveals the close relationship between exposure to pesticides and Parkinson's disease. There are no significant differences in the distribution of PON1 genotypes between cases and controls.

Fornai F, Vaglini F, Maggio R, Bonuccelli U, Corsini GU. 1997. Species differences in the role of excitatory amino acids in experimental parkinsonism. Neurosci Biobehav Rev 21(4):401-415.
Abstract: The present review discusses species differences in relation to the effects produced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); in particular, it focuses on recent evidence regarding the role of excitatory amino acids in experimental parkinsonism. The main aim of the review is to provide a phylogenetic perspective which may serve as a useful tool to study Parkinson's disease in rodents. Excitotoxicity might represent the final common pathway on which the actions of different neurotoxins, selectively directed towards nigrostriatal dompaminergic neurons, converge. This is clearly demonstrated in methamphetamine- and 6-dihydroxy-dopamine-induced parkinsonism. The role of excitotoxicity in the mechanism of action of MPTP is less clear. Although there are several species differences for MPTP it is possible to obtain in mice the same effects induced in MPTP-treated primates by combining acetaldehyde or diethyldithiocarbamate with MPTP administration. When mice are administered these combined treatments, the onset of experimental parkinsonism can be prevented using the same

pharmacological agents (i.e. glutamate N-methyl-D-aspartate antagonists) that are effective in primates. (C) 1997 Elsevier Science Ltd.

Forsberg M, Savolainen J, Jarvinen T, Leppanen J, Gynther J, Mannisto PT. 2002. Pharmacodynamic response of entacapone in rats after administration of entacapone formulations and prodrugs with varying bioavailabilities. Pharmacology & Toxicology 90(6):327-332.
Abstract: The aim of this in vivo study was to assess the effect of improved oral bioavailability of entacapone on its actual pharmacodynamic response, COMT inhibition in erythrocytes. Rats were administered entacapone orally as a suspension, as a plain solution, an entacapone/HP-beta-CD solution, two N-alkyl-carbamate ester prodrugs and intravenously as a solution. Also the relationship between pharmacodynamic and pharmacokinetic responses of entacapone was investigated. The administration of entacapone as a solution (plain solution pH 7.4; F=34.8%, or entacapone/ HP-beta-CD solution pH 3.0; F=18.5%) resulted in significantly higher degree of COMT inhibition in erythrocytes than could be achieved by administering entacapone as a suspension (pH 3.0; F=8.9%). The inhibitory E-max model did not reveal any significant differences in EC50 estimates of entacapone suspension, entacapone/HP-beta-CD solution or entacapone solution. The overall pharmacodynamic response of entacapone (AUE; area under effect-time curve) was dependent on the pharmacokinetic response (AUC; area under concentration-time curve) irrespective of the entacapone formulation and dosage form. However, this dependency did not extend to formulations producing very high peak concentrations of entacapone in plasma; high plasma concentrations reached transiently after administration of entacapone solution had only a minor effect on the overall pharmacodynamic response (AUE). The inhibitory E-max model revealed that a plateau of COMT inhibition near to E-max is attained by plasma concentrations under 2000 ng/ml, irrespective of the formulation. This supports the results concerning the dependence of AUE on AUC.

Foster A. 1999. Health research - Report revives pesticides' link to Parkinson's. Chemical Week 161(6):16.

Foster AJ, Marks L, Lock EA, Sturgess NC. 2004. Paraquat is not a substrate for the dopamine transporter and does not bind to dopamine D-1 and D-2 receptors in the rat and mouse striatum. Toxicology 202(1-2):131-132.

Frederiksen CM, Clausen J. 1999. The effects of oxidative stress in in vitro cultured astroglial cells. Atla-Alternatives to Laboratory Animals 27(3): 351-357.
Abstract: It has been suggested that glial cells in the central nervous system might function as a buffer and protect neurons and synapses. Associated with such a function, glial cells might be affected in degenerative diseases, for example, Alzheimer's disease and Parkinson's disease, due to generation of free-radicals. Free-radicals might be generated during the metabolic transformation of xenobiotics. The purpose of the present study was to determine whether a xenobiotic (in this case,

paraquat), is metabolised in glial cells during the generation of free-radicals. Furthermore, this study determined whether free-radicals can induce DNA fragmentation and whether this fragmentation can be repaired. The data produced indicated that astroglial cells contain P450-reductase which transforms paraquat into a pyridium free-radical. In turn, this causes a dose-dependent DNA fragmentation, as determined by using single-cell gel electrophoresis. The dose-dependent effect was valid up to 80 mu M paraquat. The oxidative stress induced in the astroglial cells was also associated with a maximum 15% increase in the anti-oxidative enzyme, glutathione peroxidase. After exposure to 44 mu M paraquat, followed by growth of the cells in a paraquat-free medium, DNA repair was shown to be rather slow, and was only obvious two hours after exposure to paraquat. This might be related the shuttle in which paraquat/P450-reductase is implicated, which causes a protracted generation of free-radicals. The data are discussed in relation to the available literature.

Fredriksson A, Fredriksson M, Eriksson P. 1993. Neonatal exposure to paraquat or mptp induces permanent changes in striatum dopamine and behavior in adult mice. Toxicol Appl Pharmacol 122(2):258-264.

Freeborn ER, Bloomquist JR. 2002. Inhibition of neuronal firing in murine striatal slices by cyclodiene insecticides is mediated by release of dopamine and not GABA antagonism. Pestic Biochem Physiol 73(1):59-65.
Abstract: This study investigated the effects of dieldrin and heptachlor epoxide, members of the cyclodiene class of insecticides, on neuronal firing in murine brain slices. The cyclodienes are environmentally persistent and human exposure to these compounds still occurs. Major physiological effects of cyclodienes include: (1) blockage of (3)GABA(A) receptors and (2) facilitation of neurotransmitter release with specificity for release of dopamine. Extracellular recordings were used to compare the effects of the cyclodienes to those of the prototypical GABA antagonist, picrotoxinin, on firing rates of striatal neurons. Recordings were made from cells that were inhibited by exogenously applied dopamine, which is an ideal neural substrate for differentiating effects on dopamine release from GABA antagonism. Low micromolar concentrations of cyclodiene caused depression of firing, inconsistent with GABA antagonism. Alternatively, application of picrotoxinin produced a consistent neuronal excitation in slices. The inhibitory action of dieldrin was blocked by the dopamine receptor antagonist fluphenazine, verifying the fact that cyclodiene-released dopamine was mediating the observed depression of striatal neurons. These results suggest that the ability of cyclodienes to evoke neurotransmitter release, especially dopamine, may significantly contribute to the neurotoxicity of these compounds, in vivo. (C) 2002 Elsevier Science (USA). All rights reserved.

Friedrich MR. 1999. Pesticide study aids Parkinson research. Jama-Journal of the American Medical Association 282(23):2200.

Frumkin H. 1998. Multiple system atrophy following chronic carbon disulfide exposure. Environ Health Perspect 106(9):611-613.

Abstract: Carbon disulfide toxicity is well characterized. The principal target organ is the nervous system, although cardiovascular, reproductive, ophthalmologic, and other effects are also recognized. The neurotoxicity manifests in three ways: encephalopathy, peripheral and cranial nerve dysfunction, and movement abnormalities. This report describes a case of olivopontocerebellar atrophy, a form of multiple system atrophy, developing in an adult after over 30 years of occupational exposure to carbon disulfide. The patient presented with the insidious onset of balance problems, impotence, and irritability, without tremor, cogwheel rigidity, bradykinesia, or changes in facial expression. Over the next few years severe ataxia developed, and the clinical diagnosis was confirmed with computed tomography and magnetic resonance imaging scans. The patient experienced multiple medical complications and died approximately 9 years after diagnosis. This case is consistent with a large body of clinical and experimental literature, much of it 50 years old, showing that carbon disulfide can cause movement disorders. It also serves as a reminder that movement disorders, ranging from parkinsonism to dystonia, are associated,vith a variety of toxic exposures such as manganese, carbon monoxide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and medications.

Fujikawa T, Kanada N, Shimada A, Ogata M, Suzuki I, Hayashi I, Nakashima K. 2005. Effect of sesamin in Acanthopanax senticosus HARMS on behavioral dysfunction in rotenone-induced Parkinsonian rats. Biological & Pharmaceutical Bulletin 28(1):169-172.
Abstract: The aim of this study was to determine whether sesamin, a component from Acanthopanax senticosus HARMS (ASH) pharmacologically offers protection against Parkinson's disease (PD) and its related depressive behavior in rats administered rotenone. We also examined how sesamin affected the rotenone-induced loss of tyrosine hydroxylase (TH) or glial cell line-derived neurotrophic factor (GDNF)-positive neurons in the midbrain of rats. Rats were orally administered sesamin (3, 30 mg/kg) once a day for 2 weeks before an intraperitoneal injection of rotenone (2.5 mg/kg). The pole test and catalepsy test were used to evaluate the effects of sesamin administration on bradykinesia and depressive behaviors in the PD model of rats given rotenone for 5 weeks. Those effects were compared with the ASH administrated group (250 mg/kg). Treatment with sesamin for seven weeks resulted in prophylactic effects on rotenone-induced,parkinsonian bradykinesia and catalepsy, and the effects were equivalent to ASH effects. Immunohistochemistical analysis using TH or GDNF antibody showed that sesamin provided cytoprotective effects against rotenone-induced loss of DA cells. The results suggest that it may be possible to use the ASH and sesamin for the prevention of nigral degenerative disorders, e.g., PD with depression, caused by exposure to pesticide or environmental neurotoxins in general.

Fukuda T. 2001. Neurotoxicity of MPTP. Neuropathology 21(4):323-332.
Abstract: After the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), we acquired a good animal model of Parkinson's disease. The extraordinary recent growth in knowledge using MPTP parkinsonism has fostered increased understanding of Parkinson's

disease. In the present paper, the discovery of MPTP and the biochemical, pathological, and clinical findings of MPTP parkinsonism are first reviewed briefly. Next, using MPTP parkinsonism, unresolved issuses such as the apoptosis of MPTP, levodopa toxicity, and neuroprotective effects of monoamine oxidase inhibitors or dopamine agonists are discussed. Finally, environmental factors such as the etiology of Parkinson's disease are examined. Some genetic factors that lead to familial Parkinson's disease have recently been reported, but most cases of Parkinson's disease are sporadic. Recent epidemiological evidence emphasizes an etiological relation of 18th and 19th century industrialization to Parkinson's disease. Man-made toxins, such as industrial chemicals and herbicides/pesticides, have been suggested to increase the risk of developing Parkinson's disease. I would like to highlight the significance of re-examination of environmental factors in the etiology of Parkinson's disease.

Fukui T, Hayashi Y, Kagami H, Yamamoto N, Fukuhara H, Tohnai I, Ueda M, Mizuno M, Yoshida J. 2001. Suicide gene therapy for human oral squamous cell carcinoma cell lines with adeno-associated virus vector. Oral Oncol 37 (3):211-215.
Abstract: The purpose of this study was to test the possibility of gene transfer as a new therapy for oral cancer. Adeno-associated virus (AAV) has already been used in the fields of cystic fibrosis and Parkinson's disease as a potential vector for gene therapy because of its wide host range, high transduction efficiency, and lack of cytopathogenicity. Four human oral squamous cell carcinoma cell lines were transduced with an AAV vector containing the P-galactosidase gene (AAVlacZ) in vitro. Gene transduction efficiency was from 20 to 50% at a multiplicity of infection (MOI; for the purposes of this study the number of vector genomes per target cell) of 1 x 10(3), and nearly 100% of each cell line were transduced at an MOI of 1 x 10(4). Next, four cell lines were transduced with an AAV vector containing the herpes simplex virus thymidine kinase (HSVtk) gene, which sensitizes transduced cells to ganciclovir (GCV). Subsequent administration of GCV resulted in nearly 100% tumor cell killing at an MOI of 1 x 10(4) and from 70 to 80% tumor cell killing at an MOI of 1 x 10(3). These results suggest that AAV-mediated gene transfer of HSVtk and administration of GCV has potential as a new therapy for oral squamous cell carcinoma. (C) 2001 Elsevier Science Ltd. All rights reserved.

Fukushima T. 2002 Apr. [Elucidation of paraquat poisoning mechanism and development of the neuronal death model]. Nippon Eiseigaku Zasshi 57(1): 83-6.

Fukushima T, Tanaka K, Ushijima K, Moriyama M. 2003. Retrospective study of preventive effect of maize on mortality from Parkinson's disease in Japan. Asia Pacific Journal of Clinical Nutrition 12(4):447-450.
Abstract: The findings of a negative association between past maize (Zea mays) production and current Parkinson's disease mortality by each prefecture in Japan tends to support the hypothesis that the nutritional condition that causes niacin deficiency might protect people from Parkinson's disease. Specifically, the negative association between both

the area planted for dried corn in 1960, 1970 or 1977 and the area planted for sweet corn in 1960 and age-adjusted death rates for Parkinson's disease is ecological evidence supporting the hypothesis. Extending the analysis to other cultivated crops, even stronger negative associations of age-adjusted death rates for Parkinson's disease and cultivation of rice and soybeans were found,but associations were not significant for a large variety of vegetables. The findings for soybean and rice are attributed to the correspondence (colinearity) of cultivation of these other two seed-crops with maize. Hence, further testing of the theory of niacin deprivation and prevention of Parkinson's disease finds some circumstantial support in the cultivation patterns of a grain of poor niacin and tryptophan availability.

Fukushima T, Tawara T, Isobe A, Hojo N, Shiwaku K, Yamane Y. 1995. Radical formation site of cerebral complex-i and parkinsons-disease. J Neurosci Res 42(3):385-390.
Abstract: Paraquat was reduced to the paraquat radical via complex I in bovine cerebral mitochondria and accelerated lipid peroxidation. Thirty-kilodalton subunit of complex I was considered to be the radical formation site, because of its marked destruction by the paraquat radical, The lipid peroxidation by the paraquat radical was suppressed not only by superoxide dismutase (SOD) but also by mannitol, The destruction of complex I subunits via lipid peroxidation must have been caused by the hydroxyl radical which was formed from the superoxide radical, The same phenomenon was observed by using 1-methylnicotinamide (MNA), which contains the same partial structure as paraquat in itself and is metabolized from nicotinamide in a living body, We observed NADH oxidation by MNA via cerebral complex I (Km = 26.3 mM), and MNA destroyed some complex I subunits, especially 30-kilodalton protein, Paraquat might be useful for studying the pathogenesis of Parkinson's disease (PD) in vitro, and MNA is expected to be one of the causal substances of PD from the viewpoint of the oxidative stress theory. (C) 1995 Wiley-Liss, Inc.

Galanaud JP, Elbaz A, Clavel J, Vidal JS, Corree JR, Alperovitch A, Tzourio C. 2005. Cigarette smoking and Parkinson's disease: A case-control study in a population characterized by a high prevalence of pesticide exposure. Mov Disord 20(2):181-189.
Abstract: Epidemiological studies have been consistent in showing that cigarette smoking is inversely associated with Parkinson's disease (PD), whereas pesticide use is positively associated with PD. However, the relationship between PD and cigarette smoking remains poorly understood. Our objective was to study the relationship between cigarette smoking and PD in a population characterized by a high prevalence of pesticide exposure. This case-control study was carried out among subjects enrolled in the Mutualite Sociale Agricole, the French health insurance organization for workers connected to the agricultural world. We included 247 cases and 676 controls matched on age, sex, and region of residency. Information on smoking was obtained through in-person interviews. Pesticide exposure was assessed using a case-by-case expert evaluation procedure. We found an inverse relationship between ever cigarette smoking and PD (odds ratio [OR] = 0.6; 95% confidence interval [CI] = 0.4-0.9). The strength of this

association increased with the number of pack-years. This relationship was present even when smoking was considered as long as 40 years before PD onset. An inverse association was also present among subjects professionally exposed to pesticides (OR = 0.5; 95% CI = 0.3-0.8) and was independent of the duration of exposure among men. We confirm the inverse association between cigarette smoking and PD in a population characterized by a high prevalence of professional pesticide exposure. The relationship between PD and cigarette smoking was not significantly modified or confounded by exposure to pesticides. (C) 2004 Movement Disorder Society.

Gale CR, Braidwood EA, Winter PD, Martyn CN. 1999. Mortality from Parkinson's disease and other causes in men who were prisoners of war in the Far East. Lancet 354(9196):2116-2118.
Abstract: Background During World War II, more than 140 000 Allied prisoners of war (POWs) were held captive by the Japanese in conditions of extreme privation. There have been concerns that the survivors are at increased risk of degenerative neurological disorders, especially Parkinson's disease. We assembled a cohort of British ex-POWs and analysed their mortality in a 46-year follow-up study. Methods Using records held by the War Pensions Agency, we abstracted data on 11915 British former POWs. 11134 men were traced, and observed numbers of deaths between 1952 and 1997 were compared with those expected from national rates for the male population of England and Wales. Standardised mortality ratios (SMR) were calculated. Findings Overall, mortality was lower than expected (7474 deaths vs 8796.2 expected; SMR 0.85 [95% CI 0.83-0.87]). Death rates from Parkinson's disease among the former POWs were slightly below the national average, though this difference was not statistically significant (35 deaths vs 43.2 expected; SMR 0.81 [0.56-1.13]). A similar pattern was seen for other degenerative neurological disorders (motorneuron disease 0.62 [0.31-1.11], multiple sclerosis 0.88 [0.42-1.61], and dementia 0.88 [0.68-1.11]). The former POWs had significantly lower than expected mortality from all major causes of death (ischaemic heart disease 0.81 [0.78-0.85], cerebrovascular disease 0.88 [0.81-0.95], all malignant neoplasms 0.92 [0.88-0.95], and respiratory disease 0.79 [0.74-0.85]). They also had below average rates of death from tuberculosis (0.44 [0.26-0.71]) and suicide (0.77 [0.57-1.02]), though the latter relation was not statistically significant. Mortality from diseases of the liver was increased (chronic liver disease and cirrhosis 1.68 [1.28-2.17], primary carcinoma of the liver 2.42 [1.75-3.26]). Interpretation There is little evidence that men who were POWs in the Far East have higher rates of death than the male population generally. The only exception is diseases of the liver, which may be due to infection with hepatitis B or C virus during captivity. Death-certification data cannot provide a complete picture of physical and mental health, but the period of severe malnutrition, frequent infections, exhaustion, and intense psychological stress seems not to have increased susceptibility to neurodegenerative disease.

Gao HM, Hong JS, Zhang W, Liu B. 2003 Feb 15. Synergistic dopaminergic neurotoxicity of the pesticide rotenone and inflammogen

lipopolysaccharide: relevance to the etiology of Parkinson's disease. J Neurosci 23(4):1228-36.
Abstract: Parkinson's disease (PD) is characterized by a progressive degeneration of the nigrostriatal dopaminergic pathway resulting in movement disorders. Although its etiology remains unknown, PD may be the final outcome of interactions among multiple factors, including exposure to environmental toxins and the occurrence of inflammation in the brain. In this study, using primary mesencephalic cultures, we observed that nontoxic or minimally toxic concentrations of the pesticide rotenone (0.5 nm) and the inflammogen lipopolysaccharide (LPS) (0.5 ng/ml) synergistically induced dopaminergic neurodegeneration. The synergistic neurotoxicity of rotenone and LPS was observed when the two agents were applied either simultaneously or in tandem. Mechanistically, microglial NADPH oxidase-mediated generation of reactive oxygen species appeared to be a key contributor to the synergistic dopaminergic neurotoxicity. This conclusion was based on the following observations. First, inhibition of NADPH oxidase or scavenging of free radicals afforded significant neuroprotection. Second, rotenone and LPS synergistically stimulated the NADPH oxidase-mediated release of the superoxide free radical. Third and most importantly, rotenone and LPS failed to induce the synergistic neurotoxicity as well as the production of superoxide in cultures from NADPH oxidase-deficient animals. This is the first demonstration that low concentrations of a pesticide and an inflammogen work in synergy to induce a selective degeneration of dopaminergic neurons. Findings from this study may be highly relevant to the elucidation of the multifactorial etiology of PD and the discovery of effective therapeutic agents for the treatment of the disease.

Gao HM, Hong JS, Zhang WQ, Liu B. 2002. Distinct role for microglia in rotenone-induced degeneration of dopaminergic neurons. J Neurosci 22(3):782-790.
Abstract: Increasing evidence has suggested an important role for environmental factors such as exposure to pesticides in the pathogenesis of Parkinson's disease. In experimental animals the exposure to a common herbicide, rotenone, induces features of parkinsonism; mechanistically, rotenone-induced destruction of dopaminergic neurons has been attributed to its inhibition of the activity of neuronal mitochondrial complex I. However, the role of microglia, the resident brain immune cells in rotenone-induced neurodegeneration, has not been reported. Using primary neuron-enriched and neuron/glia cultures from the rat mesencephalon, we discovered an extraordinary feature for rotenone-induced degeneration of cultured dopaminergic neurons. Although little neurotoxicity was detected in neuron-enriched cultures after treatment for 8 d with up to 20 nM rotenone, significant and selective dopaminergic neurodegeneration was observed in neuron/glia cultures 2 d after treatment with 20 nM rotenone or 8 d after treatment with 1 nM rotenone. The greatly enhanced neurodegenerative ability of rotenone was attributed to the presence of glia, especially microglia, because the addition of microglia to neuron-enriched cultures markedly increased their susceptibility to rotenone. Mechanistically, rotenone stimulated the release

of superoxide from microglia that was attenuated by inhibitors of NADPH oxidase. Furthermore, inhibition of NADPH oxidase or scavenging of superoxide significantly reduced the rotenone-induced neurotoxicity. This is the first report demonstrating that microglia play a pivotal role in rotenone-induced degeneration of dopaminergic neurons. The results of this study should advance our understanding of the mechanism of action for pesticides in the pathogenesis of Parkinson's disease.

Gao HM, Hong JS, Zhang WQ, Liu B. 2003. Synergistic dopaminergic neurotoxicity of the pesticide rotenone and inflammogen lipopolysaccharide: Relevance to the etiology of Parkinson's disease. J Neurosci 23(4):1228-1236.
Abstract: Parkinson's disease (PD) is characterized by a progressive degeneration of the nigrostriatal dopaminergic pathway resulting in movement disorders. Although its etiology remains unknown, PD may be the final outcome of interactions among multiple factors, including exposure to environmental toxins and the occurrence of inflammation in the brain. In this study, using primary mesencephalic cultures, we observed that nontoxic or minimally toxic concentrations of the pesticide rotenone (0.5 nM) and the inflammogen lipopolysaccharide (LPS) (0.5 ng/ml) synergistically induced dopaminergic neurodegeneration. The synergistic neurotoxicity of rotenone and LPS was observed when the two agents were applied either simultaneously or in tandem. Mechanistically, microglial NADPH oxidase-mediated generation of reactive oxygen species appeared to be a key contributor to the synergistic dopaminergic neurotoxicity. This conclusion was based on the following observations. First, inhibition of NADPH oxidase or scavenging of free radicals afforded significant neuroprotection. Second, rotenone and LPS synergistically stimulated the NADPH oxidase-mediated release of the superoxide free radical. Third and most importantly, rotenone and LPS failed to induce the synergistic neurotoxicity as well as the production of superoxide in cultures from NADPH oxidase-deficient animals. This is the first demonstration that low concentrations of a pesticide and an inflammogen work in synergy to induce a selective degeneration of dopaminergic neurons. Findings from this study may be highly relevant to the elucidation of the multifactorial etiology of PD and the discovery of effective therapeutic agents for the treatment of the disease.

Gao HM, Liu B, Hong JS. 2003. Critical role for microglial NADPH oxidase in rotenone-induced degeneration of dopaminergic neurons. J Neurosci 23 (15):6181-6187.
Abstract: Increasing evidence has suggested an important role for environmental toxins such as pesticides in the pathogenesis of Parkinson's disease (PD). Chronic exposure to rotenone, a common herbicide, reproduces features of Parkinsonism in rats. Mechanistically, rotenone-induced dopaminergic neurodegeneration has been associated with both its inhibition of neuronal mitochondrial complex I and the enhancement of activated microglia. Our previous studies with NADPH oxidase inhibitors, diphenylene iodonium and apocynin, suggested that NADPH oxidase-derived superoxide might be a major factor in mediating the microglia-enhanced rotenone neurotoxicity. However, because of the relatively low

specificity of these inhibitors, the exact source of superoxide induced by rotenone remains to be further determined. In this study, using primary mesencephalic cultures from NADPH oxidase - null ( gp91(phox-/-)) or wild-type (gp91(phox+/+)) mice, we demonstrated a critical role for microglial NADPH oxidase in mediating microglia-enhanced rotenone neurotoxicity. In neuron-glia cultures, dopaminergic neurons from gp91 (phox-/-) mice were more resistant to rotenone neurotoxicity than those from gp91(phox+/+) mice. However, in neuron-enriched cultures, the neurotoxicity of rotenone was not different between the two types of mice. More importantly, the addition of microglia prepared from gp91(phox+/+) mice but not from gp91(phox-/-) mice to neuron-enriched cultures markedly increased rotenone-induced degeneration of dopaminergic neurons. Furthermore, apocynin attenuated rotenone neurotoxicity only in the presence of microglia from gp91(phox-/-) mice. These results indicated that the greatly enhanced neurotoxicity of rotenone was attributed to the release of NADPH oxidase-derived superoxide from activated microglia. This study also suggested that microglial NADPH oxidase may be a promising target for PD treatment.

Gao HM, Liu B, Zhang WQ, Hong JS. 2003. Novel anti-inflammatory therapy for Parkinson's disease. Trends Pharmacol Sci 24(8):395-401.
Abstract: Parkinson's disease (PD) is a movement disorder that is characterized by progressive degeneration of the nigrostriatal dopamine system. Although dopamine replacement can alleviate symptoms of the disorder, there is no proven therapy to halt the underlying progressive degeneration of dopamine-containing neurons. Recently, increasing evidence from human and animal studies has suggested that neuroinflammation is an important contributor to the neuronal loss in PD. Moreover, the pro-inflammatory agent lipopolysaccharide itself can directly initiate degeneration of dopamine-containing neurons or combine with other environmental factor(s), such as the pesticide rotenone, to exacerbate such neurodegeneration. These effects provide strong support for the involvement of inflammation in the pathogenesis of PD. Furthermore, growing experimental evidence demonstrates that inhibition of the inflammatory response can, in part, prevent degeneration of nigrostriatal dopamine-containing neurons in several animal models of PD, suggesting that inhibition of inflammation might become a promising therapeutic intervention for PD.

Garcia-Garcia F, Ponce S, Brown R, Cussen V, Krueger JM. 2005. Sleep disturbances in the rotenone animal model of Parkinson disease. Brain Res 1042(2):160-168.
Abstract: Parkinson disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the presence of intracytoplasmatic inclusions known as Lewy bodies. Chronic administration of rotenone (RT) produces Parkinson's-like symptoms in rats. Because PD patients have disrupted sleep patterns, we determined if chronic RT administration produces similar changes in rat sleep. RT was administered for 28 days to rats. Basal and vehicle (VH) rats received saline or dimethyl sulfoxide and polyethylene glycol (1:1), respectively. VH

infusion induced a progressive decrease in non-rapid eye movement sleep (NREMS) during the 4-week period of VH infusion and REMS was reduced in the third and fourth week of VH infusion. VH infusion did not induce dopaminergic cell degeneration. Rats receiving RT infusion also showed decreased NREMS during the treatment. REMS was dramatically reduced on day 7 although subsequently on days 13 and 20 REMS was similar to basal values. After 4 weeks of RT infusion, time in REMS was decreased again. In RT-treated rats, progressive dopaminergic cell degeneration occurred in the SNc. After 4 weeks of daily injections of L-dopa in RT infused rats, NREMS values remained similar to those values obtained after RT alone. L-dopa therapy did, however, induce a recovery of REMS in weeks 3 and 4 of RT infusion. Dopaminergic cell damage persisted in the L-dopa-RT-infused rats. We conclude that the RT-PD rat model is associated with large long-terra sleep disruption, however, the vehicle, DMSO/PEG had as large an effect as RT on sleep, thus changes in sleep cannot be ascribed to loss of dopaminergic cells. Such results question the validity of the RT-PD rat model. © 2005 Elsevier B.V All rights reserved.

Garcia-Garcia FA, Cussen VA, Krueger JM. 2003. Sleep disturbances in the rotenone-animal model of Parkinson disease. Sleep 26:A332.

Garrels L, Folkerts H. 1996 Aug. [Parkinson syndrome after CO poisoning. Unexpected late manifestation and favorable prognosis]. Nervenarzt 67(8): 682-5.
Abstract: Although individual extrapyramidal symptoms as a consequence of carbon monoxide intoxication have frequently been reported, typical (complete) Parkinson's syndrome has very rarely been documented. This report presents for the first time a case of acute Parkinson's syndrome with delayed manifestation after the initially occurring organic psychosis. A 53-year-old man with a long history of schizoaffective psychosis first developed a severe acute organic psychosis with disturbances of orientation and marked amnestic disturbances after carbon monoxide intoxication as a result of a suicide attempt. On the 21st day after intoxication, acute Parkinson's syndrome with right accentuation was recorded, with CCT identification of lesions on both sides of the basal ganglia area. Full remission of the Parkinson's syndrome was achieved with rheological treatment and L-dopa therapy.

Gartner CE, Battistutta D, Dunne MP, Silburn PA, Mellick GD. 2005. Test-retest repeatability of self-reported environmental exposures in Parkinson's disease cases and healthy controls. Parkinsonism & Related Disorders 11 (5):287-295.
Abstract: There is substantial disagreement among published epidemiological studies regarding environmental risk factors for Parkinson's disease (PD). Differences in the quality of measurement of environmental exposures may contribute to this variation. The current study examined the test-retest repeatability of self-report data on risk factors for PD obtained from a series of 32 PD, cases recruited from neurology clinics and 29 healthy sex-, age- and residential suburb-matched controls. Exposure data were collected in face-to-face interviews using a

structured questionnaire derived from previous epidemiological studies. High repeatability was demonstrated for 'lifestyle' exposures, such as smoking and coffee/tea consumption (kappas 0.70-1.00). Environmental exposures that involved some action by the person, such as pesticide application and use of solvents and metals, also showed high repeatability (kappas > 0.78). Lower repeatability was seen for rural residency and bore water consumption (kappa 0.39-0.74). In general, we found that case and control participants provided similar rates of incongruent and missing responses for categorical and continuous occupational, domestic, lifestyle and medical exposures. (C) 2005 Elsevier Ltd. All rights reserved.

Gasparini M, Caldora G, Fabrizio E, Di Rezze S, Vanacore N, Meco G. 2004. Parkinson's disease and pesticide exposure: Does a selective cognitive profile exist? Mov Disord 19:S411.

Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D. 2001. Environmental pesticide exposure as a risk factor for Alzheimer's disease: A case-control study. Environ Res 86(1):37-45.
Abstract: The aim of this study was to evaluate the influence of pesticide exposure on the development of Alzheimer's disease (AD), taking into account the potentially confounding factors (genetic, occupational exposure, and sociodemographic). The 1924 study participants (> 70 years old) were randomly selected in the Saguenay-Lac Saint-Jean region (Quebec, Canada). The AD diagnosis was established in three steps according to recognized criteria. Sixty-eight cases were paired with a nondemented control for age (+/-2 years) and sex. Structured questionnaires addressed to subjects and proxy respondents allowed a description of the sociodemographic characteristics, lifestyle characteristics, and residential, occupational, familial, and medical histories. Assessment of environmental exposure to pesticides was based on residential histories and the agriculture census histories of Statistics Canada (1971-1991) for herbicide and insecticide spraying in the area. Statistical analyses were performed with a logistic regression, adjusting for potential confounding factors. The results failed to show a significant risk of AD with an exposure to herbicides, insecticides, and pesticides. However, future investigations are needed to establish more precisely the identification, measurement, mobility, and bioavailability of neurotoxic pesticide residues in relation to AD. (C) 2001 Academic Press.

Gelinas S, Bureau G, Valastro B, Massicotte G, Cicchetti F, Chiasson K, Gagne B, Blanchet J, Martinoli MG. 2004. Alpha and beta estradiol protect neuronal but not native PC12 cells from paraquat-induced oxidative stress. Neurotoxicity Research 6(2):141-148.
Abstract: Oxidative stress is currently considered a mediator of cell death in several neurodegenerative diseases. Notably, it may play an important role in the degeneration of dopamine neurons of the substantia nigra in Parkinson's disease. We examined the effect of a strong oxidant, the herbicide paraquat, on cell distress using native and neuronal pheochromocytoma PC12 cells. Paraquat administration for 8 hours induced a significant cellular death in both native and in neuronal PC12

cells. Since the anti-oxidant properties of estrogens may promote neuroprotection in vitro and in vivo, we then investigated the ability of estradiol stereoisomers,17alpha-estradiol and 17beta-estradiol, to rescue PC12 cells submitted to paraquat-induced oxidative stress. Our results show a protective effect of both estradiol stereoisomers in neuronal PC12 cells treated with paraquat, whereas this effect could not be observed in native PC12 cells. We also demonstrate that estrogen receptor beta protein expression is modulated by paraquat administration in native PC12 cells, while paraquat does not change estrogen receptor beta expression in neuronal PC12 cells. Paraquat also decreases estrogen receptor alpha in neuronal PC12 cells, thus suggesting new routes for paraquat to collapse cellular metabolism. Besides, the oxidation of dihydrodhodamine-123 into fluorescent rhodamine in the presence of paraquat but not in presence of paraquat and 17alpha-estradiol or 17beta-estradiol, sustain a possible direct scavenging role of both estradiol stereoisomers.

Gerber GB, Leonard A, Hantson P. 2002. Carcinogenicity, mutagenicity and teratogenicity of manganese compounds. Crit Rev Oncol Hematol 42(1): 25-34.
Abstract: Manganese, an essential trace element, is one of the most used metals in the industry. Recently, several new manganese compounds have been introduced as fungicide, as antiknock agent in petrol and as contrasting agent in nuclear magnetic resonance tomography. Manganese displays a somewhat unique behaviour with regard to its toxicity. It is relatively non-toxic to the adult organism except to the brain where it causes Parkinson-like symptoms when inhaled even at moderate amounts over longer periods of time. Relatively high doses of manganese affect DNA replication and repair in bacteria and causes mutations in microorganism and mammalian cells although the Ames test does not appear to be particularly responsive to manganese. In mammalian cells, manganese causes DNA damage and chromosome aberrations. Information on organic manganese derivatives is still insufficient. Large amounts of manganese affect fertility in mammals and are toxic to the embryo and foetus. The fungicide MANEB and the contrasting agent MnDPDP also can be embryotoxic, but the latter only at doses much higher than those clinically employed, Information on the anti-knock agent MMT is inadequate. On the other hand, manganese deficiency can also affect fertility and be teratogenic. Information on cancer due to manganese is scanty but the results available do not indicate that inorganic manganese is carcinogenic. More information is desirable with regard to the organic manganese derivatives. It may surprise that an agent that causes mutations is not also carcinogenic. The experience with manganese shows that conclusions with regard to carcinogenicity of an agent based on the observation of mutations are subject to uncertainties. Altogether, it appears that, because of the very high doses at which positive effects hake been found, manganese would not represent a significant carcinogenic risk to the population and workers. Care must, however, be exercised with respect to central-nervous symptoms after chronic exposure and with respect to effects on the embryo. Pregnant women should not be exposed

to manganese at the work place. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Gerlach M, Riederer P, Youdim MBH. 1992. The molecular pharmacology of l-deprenyl. European Journal of Pharmacology-Molecular Pharmacology Section 226(2): 97-108.
Abstract: L-Deprenyl, the selective inhibitor of monoamine oxidase type B (MAO-B), has gained wide acceptance as a useful form of adjunct therapeutic drug in the treatment of Parkinson's disease. This review summarizes the molecular pharmacology of L-deprenyl, and the advances in our understanding of its possible mode of action in Parkinson's disease. L-Deprenyl belongs to the class of enzyme-activated irreversible inhibitors also described as 'suicide' inhibitors, because the compound acts as a substrate for the target enzyme, whose action on the compound results in irreversible inhibition. L-Deprenyl first of all forms a noncovalent complex with MAO as an initial, reversible step. The subsequent interaction of L-deprenyl with MAO leads to a reduction of the enzyme-bound flavine-adenine dinucleotide (FAD), and concomitant oxidation of the inhibitor. This oxidized inhibitor then reacts with FAD at the N-5-position in a covalent manner. The observed in vitro selectivity of L-deprenyl for MAO-B may be accounted for by differences in the affinities of the two MAO subtypes for reversible interaction with L-deprenyl, differences in the rates of reaction within the noncovalent complexes to form the irreversibly inhibited adduct, or a combination of both these factors. However, if selective inhibition is to be maintained in vivo, correct dosage schedules are critically important, since all selective MAO inhibitors described up to now lack selectivity at high doses. In experimental animals L-deprenyl is protective against the damaging effects of several neurotoxins, including the dopaminergic agents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) and the noradrenergic neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4). Beside MAO-B inhibition, which above all explains the prevention of neurotoxic action of MPTP by preventing its metabolism, L-deprenyl appears to exhibit other mechanisms of action which are independent of its action on MAO-B.

Gerlach M, Youdim MBH, Riederer P. 1996. Pharmacology of selegiline. Neurology 47(6):S137-S145.
Abstract: The acetylenic selective monoamine oxidase (MAO) type B suicide inhibitor selegiline (previously called L-deprenyl) has proved to be a useful adjuvant to levodopa therapy and monotherapy of Parkinson's disease (PD). Selegiline is readily absorbed from the gastrointestinal tract and rapidly enters the brain and spinal cord following oral administration. The drug binds to brain regions with a high MAO-B content, such as the thalamus, the striatum, the cortex, and the brainstem. It is extensively metabolized in humans, mainly in the liver, to form desmethylselegiline and methamphetamine, which are further metabolized to amphetamine. Eighty-six percent of the 10-mg dose was recovered in the urine within 24 hours. These data suggest that accumulation of metabolites does not occur. Although not all features of its anti-PD action are known, studies using brain obtained at autopsy from patients who had been treated with

10 mg of selegiline showed that selective inhibition of MAO-B, with the concomitant increase of phenylethylamine and dopamine (DA) but not of serotonin or noradrenaline, in the basal ganglia may be regarded as its mode of action. The protective effects afforded by selegiline in PD, resulting in a delayed need for levodopa therapy, have been variously interpreted in terms of the involvement of an endogenous neurotoxin or an oxygen free radical mechanism (oxidative stress) in the development of PD. However, although many different hypotheses have been advanced and recent findings have emphasized the significance of oxidative stress in the pathogenesis of the disease, the cause of chronic nigral cell death and the underlying mechanisms remain, as yet, elusive. Therefore, there is no clear knowledge regarding an understanding of the reported effects of selegiline on the progression of PD. Nevertheless, selegiline might be expected to have some protective effects in reducing the production of potentially neurotoxic compounds resulting in the MAO-catalyzed oxidation of DA. In addition, some evidence suggests both an indirect (via induction of radical-scavenging enzymes) and a direct antioxidant function for selegiline. On the other hand, the reported protective effect of selegiline might also receive a contribution from the diminished potentiation of the N-methyl-D-aspartate receptor by the polyamine binding site. Finally, the effects of selegiline might also involve preventing, or perhaps to some extent reversing, the decline in resistance normally associated with cellular aging because of its neurotrophine-like action. However, even in the early clinical stage of PD, the sequence of events leading to nigral cell death may be too far advanced for selegiline to exhibit its maximum potential.

Giasson BI, Lee VMY. 2000. A new link between pesticides and Parkinson's disease. Nat Neurosci 3(12):1227-1228.
Abstract: Environmental factors are thought to be an important cause od Parkinson's disease, a new study shows that rats chronically treated with the mitochondrial inhibitor rotenone, a common pesticide, develop neuropathological and behavioral symptoms sf Parkinsonism.

Gille G, Hung ST, Reichmann H, Rausch WD. 2004. Oxidative Stress to Dopaminergic Neurons as Models of Parkinson's DiseaseVolume 1018. p 533-540. Stress: Current Neuroendocrine and Genetic Approaches: Annals of the New York Academy of Sciences.
Abstract: The effects of exogenous toxins (MPP+, rotenone) and potentially neurotoxic properties of levodopa (L-DOPA) on the survival rate of dopaminergic neurons in dissociated primary culture are presented. Dopamine agonists show a capacity to counteract MPP+-toxicity. Moreover, a preserving potential of the antioxidant and bioenergetic coenzyme Q(10) (CoQ(10)) on the activities of tyrosine hydroxylase (TH), complexes I and II of the respiratory chain, and hexokinase activity in striatal slice cultures against MPP+ is demonstrated.

Gillette JS, Bloomquist JR. 2003. Differential up-regulation of striatal dopamine transporter and alpha-synuclein by the pyrethroid insecticide permethrin. Toxicol Appl Pharmacol 192(3):287-293.
Abstract: The effects of permethrin on striatal dopaminergic biomarkers

were assessed in this study. Retired breeder male C57 B1/6 mice were given an ip dose of permethrin (0.1-200 mg/kg) at 7-day intervals, over a 2-week period (Days 0, 7, and 14). Animals were then sacrificed 1 day (t = 1), 14 days (t = 14), or 28 days after the last treatment (t = 28). Dopamine transporter (DAT) protein as assayed by Western blotting was increased to 115% in the 0.8 mg/kg group over that of control mice at t = 1 ($P < 0.05$). At t = 14, this value increased to 140% of control, and declined slightly to 133% of control at t = 28. The mice given the 1.5 mg/kg dose displayed a significant increase in DAT protein only at t = 28, to 145% of controls. Thus, upregulation of the DAT at low doses of PM is variable 24 h after treatment, and seems to stabilize by t = 28. The threshold dose for increasing DAT expression in Western blots by t = 28 was 0.2 mg/kg permethrin. [H-3]GBR 12935, used to assay DAT binding, followed the same trend as that for the Western blotting data for 0.8 and 1.5 mg/kg doses of permethrin over the 4 weeks posttreatment. At 200 mg/kg permethrin, DAT protein was unchanged vs controls (t = 1), but had significantly increased by t = 14 and continued to increase at t = 28, suggesting that the reduced dopamine transport at this dose was due to nerve terminal stress and that recovery had occurred. The protein a-synuclein was also significantly induced at the 1.5 mg/kg dose at t = 1; however, unlike DAT up-regulation, this effect had declined to control values by t = 14. Maximal induction of a-synuclein protein occurred at a dose of 50 mg/kg permethrin. These data provide evidence that the pyrethroid class of insecticides can modulate the dopaminergic system at low doses, in a persistent manner, which may render neurons more vulnerable to toxicant injury. 

GILLHESPY RO. 1958 Mar. Methylpentynol carbamate in the management of insomnia and parkinsonism. Br J Clin Pract 12(3):191-3.

Gluck M, Ehrhart J, Jayatilleke E, Zeevalk GD. 2002. Inhibition of brain mitochondrial respiration by dopamine: involvement of H2O2 and hydroxyl radicals but not glutathione-protein-mixed disulfides. J Neurochem 82(1): 66-74.
Abstract: Examination of the downstream mediators responsible for inhibition of mitochondrial respiration by dopamine (DA) was investigated. Consistent with findings reported by others, exposure of rat brain mitochondria to 0.5 mm DA for 15 min at 30degreesC inhibited pyruvate/glutamate/malate-supported state-3 respiration by 20%. Inhibition was prevented in the presence of pargyline and clorgyline demonstrating that mitochondrial inhibition arose from products formed following MAO metabolism and could include hydrogen peroxide (H2O2), hydroxyl radical, oxidized glutathione (GSSG) or glutathione-protein mixed disulfides (PrSSG). As with DA, direct incubation of intact mitochondria with H2O2 (100 mum) significantly inhibited state-3 respiration. In contrast, incubation with GSSG (1 mm) had no effect on O-2 consumption. Exposure of mitochondria to 1 mm GSSG resulted in a 3.3-fold increase in PrSSG formation compared with 1.4- and 1.5-fold increases in the presence of 100 mum H2O2 or 0.5 mm DA, respectively, suggesting a dissociation between PrSSG formation and effects on respiration. The lack of inhibition

of respiration by GSSG could not be accounted for by inadequate delivery of GSSG into mitochondria as increases in PrSSG levels in both membrane-bound (2-fold) and intramatrix (3.5-fold) protein compartments were observed. Furthermore, GSSG was without effect on electron transport chain activities in freeze-thawed brain mitochondria or in pig heart electron transport particles (ETP). In contrast, H2O2 showed differential effects on inhibition of respiration supported by different substrates with a sensitivity of succinate > pyruvate/malate > glutamate/ malate. NADH oxidase and succinate oxidase activities in freeze-thawed mitochondria were inhibited with IC50 approximately 2-3-fold higher than in intact mitochondria. ETPs, however, were relatively insensitive to H2O2 . Co-administration of desferrioxamine with H2O2 had no effect on complex I-associated inhibition in intact mitochondria, but attenuated inhibition of rotenone-sensitive NADH oxidase activity by 70% in freeze-thawed mitochondria. The results show that DA-associated inhibition of respiration is dependent on MAO and that H-2 O-2 and its downstream hydroxyl radical rather than increased GSSG and subsequent PrSSG formation mediate the effects.

Gluck MR, Krueger MJ, Ramsay RR, Sablin SO, Singer TP, Nicklas WJ. 1994. Characterization of the inhibitory mechanism of 1-methyl-4-phenylpyridinium and 4-phenylpyridine analogs in inner membrane preparations . J Biol Chem 269(5):3167-3174.
Abstract: We have investigated the mechanism of the inhibition of membrane-bound NADH dehydrogenase by 1-methyl-4-phenylpyridinium (MPP+) and a series of its 4'-alkyl-substituted analogs of increasing hydrophobicity, as well as their neutral, desmethyl congeners. Comparison of hydrophobicity, as measured by partition coefficients, with the IC50 for the inhibition of NADH oxidase activity in mitochondrial inner membrane preparations shows a negative correlation, but the cationic inhibitors are more effective than the neutral analogs with similar hydrophobicity. The presence of 10 mum tetraphenylboron (TPB-) potentiates the inhibitory power of positively charged analogs up to 4'-pentyl-MPP', while the neutral inhibitors are unaffected by TPB-. Without TPB-, the more hydrophilic analogs give incomplete inhibition, but the inclusion of TPB- permits the attainment of complete inhibition, accompanied by the appearance of sigmoidal titration curves. These data support the hypothesis that MPP+ analogs, like rotenone, are bound at two sites on the enzyme and occupancy of both is required for complete inhibition. TPB-, by forming ion pairs with the cationic analogs, facilitates their equilibration to both sites in membrane preparations. When present in molar excess over the MPP+ analog, TPB- partially reverses the inhibition by decreasing its concentration in the more hydrophilic binding site. The effect of temperature and of pH on the IC50 values for inhibition support the concept of dual binding sites, and the pH dependence of the inhibition reveals the participation of two ionized protein groups in the binding, one of which may be a thiol group.

Goers J, Manning-Bog AB, Mccormack AL, Millett IS, Doniach S, Di Monte DA, Uversky VN, Fink AL. 2003. Nuclear localization of alpha-synuclein and its

interaction with histones. Biochemistry (Mosc) 42(28):8465-8471.
Abstract: The aggregation of alpha-synuclein is believed to play an important role in the pathogenesis of Parkinson's disease as well as other neurodegenerative disorders ("synucleinopathies"). However, the function of alpha-synuclein under physiologic and pathological conditions is unknown, and the mechanism of alpha-synuclein aggregation is not well understood. Here we show that alpha-synuclein forms a tight 2:1 complex with histories and that the fibrillation rate of alpha-synuclein is dramatically accelerated in the presence of histories in vitro. We also describe the presence of cc-synuclein and its co-localization with histories in the nuclei of nigral neurons from mice exposed to a toxic insult (i.e., injections of the herbicide paraquat). These observations indicate that translocation into the nucleus and binding with histones represent potential mechanisms underlying alpha-synuclein pathophysiology.

Golbe LI, Farrell TM, Davis PH. 1990. Follow-up study of early-life protective and risk factors in Parkinson's disease. Mov Disord 5(1):66-70.
Abstract: Previous studies suggest that Parkinson's disease (PD) is negatively associated with early-life intake of vitamin E-rich foods and positively associated with rural experience. Using a new survey design, we attempted to confirm and extend these results. We gave a telephone questionnaire to 106 patients with PD and to their spouses as controls. It assessed premarital consumption of 31 foods of various vitamin E content, vitamin supplements, and exposure to rural living. Respondents rated food consumption with respect to what they perceived as the average for their sex and age at that time. We found female patients with PD less likely than spouses to have eaten "peanuts and peanut butter" (p less than .05), which are high in vitamin E. "Salad with dressing," also high in vitamin E, gave a similar result (p less than .05) for a male-predominant patient group. Separate comparison of male controls with female controls ruled out sex-related preferences as the explanation of our findings. Patients had more extensive rural experience and were more likely to have frequently sprayed pesticides (p less than .05) than had controls. Our results justify further investigations into early-life vitamin E intake, pesticides, and neurotoxins associated with rural life.

Golbe LI, Rubin RS, Cody RP, Belsh JM, Duvoisin RC, Grosmann C, Lepore FE, Mark MH, Sachdeo RC, Sage JI, Zimmerman TR. 1996. Follow-up study of risk factors in progressive supranuclear palsy. Neurology 47(1):148-154.
Abstract: The cause of progressive supranuclear palsy (PSP) is not known and has been little studied. The one previous controlled epidemiologic survey, performed at our center in 1986, found small-town experience and greater educational attainment as PSP risks, but, in retrospect, these results may have been produced by ascertainment bias. Since that time, several anecdotal reports have implicated heredity and various environmental exposures in the cause of some cases of PSP. To clarify the results of the previous study and to evaluate the more recently implicated candidate factors in a controlled fashion, we mailed a validated 69-item questionnaire to 91 personally examined patients with PSP and 104 unmatched controls with other neurologic conditions for which they had

been referred to our tertiary neurologic center. We were able to match 75 subjects from each group by year of birth, sex, and race and subjected them to a separate matched-pair analysis. We allowed surrogates to supply any or all of the responses. Questions concerned hydrocarbon, pesticide, and herbicide exposure; urban/rural living; auto repair and other occupations; head trauma; educational attainment; maternal age; and family history of PSP, parkinsonism, dementia, and other neurologic conditions. A statistically significant finding was that patients with PSP there less likely to have completed at least 12 years of school (matched odds ratio = 0.35, 95% CI = 0.12-0.95, p = 0.022; unmatched odds ratio = 0.44, 95% CI = 0.21-0.89, p = 0.020). We hypothesize that this result may be a proxy for poor early-life nutrition or for occupational or residential exposure to an as-yet unsuspected toxin. Future studies should examine these potential risk factors in PSP.

Gonzalez-Polo RA, Rodriguez-Martin A, Moran JM, Niso M, Soler G, Fuentes JM. 2004. Paraquat-induced apoptotic cell death in cerebellar granule cells. Brain Res 1011(2):170-176.
Abstract: We examined the toxicity of paraquat, a possible environmental risk factor for neurodegenerative disorders like Parkinson's disease (PD). Paraquat is structurally similar to the neurotoxin MPP+ that can induce Parkinsonian-like features in rodents, non-human primates and human. Exposure of cerebellar granule cells to relatively low concentrations of paraquat (5 muM) produces apoptotic cell death with a reduction in mitochondrial cytochrome c content, proteolytic activation and caspase-3 activity increase and DNA fragmentation. Paraquat-induced apoptosis was significantly attenuated by co-treatment of cerebellar granule cells with the radical scavenger vitamin E, suggesting that paraquat-induced free radicals serve as important signal in initiation of cell death. As a decrease in mitochondrial cytochrome c content is also prevented by allopurinol, we suggest that xanthine oxidase plays an important role in the free radical production that precedes the apoptotic cascade and cell death after paraquat exposition. (C) 2004 Elsevier B.V. All rights reserved.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL. 1996. Exposure to heavy metals and pesticides as risk factors for Parkinson's disease: A case-control study. Neurology 46(2 ):27005.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. 1998. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 50(5):1346-1350.
Abstract: We assessed exposure to pesticides, farming, well water use, and rural living as risk factors for Parkinson's disease (PD) in a population-based case-control study consisting of men and women greater than or equal to 50 years of age who had primary medical care at Henry Ford Health System in metropolitan Detroit. Enrolled PD patients (n = 144) and control subjects (n = 464) were frequency-matched for age, race, and sex. When adjusted for these variables and smoking status, there was a significant association of occupational exposure to herbicides (odds ratio [OR], 4.10; 95% CI, 1.37, 12.24) and insecticides (OR, 3.55; 95% CI, 1.75,

7.18) with PD, but no relation was found with fungicide exposure. Farming as an occupation was significantly associated with PD (OR, 2.79; 95% CI, 1.03, 7.55), but there was no increased risk of the disease with rural or farm residence or well water use. The association of occupational exposure to herbicides or insecticides with PD remained after adjustment for farming. The association of farming with PD was maintained after adjustment for occupational herbicide exposure and was of borderline significance after adjustment for occupational insecticide exposure. These results suggest that PD is associated with occupational exposure to herbicides and insecticides and to farming and that the risk, of farming cannot be accounted for by pesticide exposure alone.

Gorell JM, Peterson EL, Rybicki BA, Johnson CC. 2004. Multiple risk factors for Parkinson's disease. J Neurol Sci 217(2):169-174.
Abstract: Objective: To determine the relative contribution of various risk factors to the development of Parkinson's disease (PD). Methods: Ten variables that were independently associated with PD in a health system population-based case-control study of epidemiological risk factors for the disease were jointly assessed. Stepwise logistic regression, adjusted for sex, race and age was used to develop a multiple variate model that best predicted the presence of PD. The population attributable risk was estimated for each variable in the final model, as well as for all factors together. Results: The 10 initial variables included >20 years occupational exposure to manganese or to copper, individually; >20 years joint occupational exposure to either lead and copper, copper and iron, or lead and iron; a positive family history of PD in first- or second-degree relatives; occupational exposure to insecticides or herbicides; occupational exposure to farming; and smoking. Logistic regression resulted in a final model that included >20 years joint occupational exposure to lead and copper (p = 0.009; population attributable risk [PAR] = 3.9%), occupational exposure to insecticides (p = 0.002; PAR = 8.1%), a positive family history of PD in first- and second-degree relatives (p = 0.001; PAR = 12.4%), and smoking :5 30 pack-years or not smoking (p = 0.005; PAR = 41.4%). All four variables combined had a PAR = 54.1%. Conclusions: Our final model of PD risk suggests that occupational, environmental lifestyle and, likely, genetic factors, individually and collectively, play a significant role in the etiology of the disease. Clearly, additional risk factors remain to be determined through future research. (C) 2003 Elsevier B.V. All rights reserved.

Gorkin V, Amanov K, Mamadiev M, Medvedev A, Khuzhamberdiev M. 1994. The biochemical-mechanisms of the toxic effects of some pyridine-derivatives . 1. Study on the deamination of biogenic-amines and other nitrogenous compounds in paraquat intoxication. Arch Environ Contam Toxicol 26(4): 534-539.
Abstract: Lethal intoxication of rats with the herbicide paraquat (1,1'-dimethyl-4,4'-bipyridilium dichloride) caused a stimulation of lipid peroxidation (LPO) in lung, brain, heart, liver, and kidney. Treatment of animals with antioxidant diludin (2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine) or with the reductants sodium ascorbate or thiosulphate

normalized the rate of LPO in these tissues and decreased mortality of intoxicated rats. The development of lethal paraquat intoxication was accompanied by a decrease of the deamination of monoamine oxidase (MAO) substrates serotonin, tryptamine, benzylamine, and tyramine in mitochondria of organs studied with simultaneous stimulation or appearance of deamination of glucosamine, gamma-aminobutyric acid (GABA), putrescine, and L-lysine. The alterations in deamination of the nitrogenous compounds caused by paraquat were also reversed by treatment of animals with antioxidant or reductants. The data obtained support a hypothesis of an involvement of modification in catalytic properties of MAOs in the pathogenesis of paraquat intoxication.

Gotz ME, Dirr A, Burger R, Janetzky B, Weinmuller M, Chan WW, Chen SC, Reichmann H, Rausch WD, Riederer P. 1994. Effect of lipoic acid on redox state of coenzyme-q in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and diethyldithiocarbamate. European Journal of Pharmacology-Molecular Pharmacology Section 266(3):291-300. Abstract: We investigated the effects of a combined treatment of male C57Bl/6 mice with diethyldithiocarbamate and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the absence or presence of different forms of lipoic acid (Thioctacid T(R). commonly used for treatment of diabetic polyneuropathies) on levels and redox states of alpha-tocopherol and coenzyme Q in vivo and on activities of various enzymes of energy metabolism ex vivo. Treatment of mice with diethyldithiocarbamate plus MPTP resulted in a decrease in dopamine (67%) and its major metabolites dihydroxyphenylacetic acid (38%) and homovanillic acid (37%) in striatum. alpha-Tocopherol levels were unaltered in striatum; however, the reduced forms of coenzyme Q were decreased in frontal cortex and hippocampus following diethyldithiocarbamate plus MPTP. In frontal cortex activity of NADH dehydrogenase was significantly inhibited by diethyldithiocarbamate plus MPTP ex vivo, suggesting that the neurotoxic metabolite of MPTP, 1-methyl-4-phenylpyridinium ion, is acting in brain regions other than striatum as well. Lipoic acid, administered 6 times, each at 90 min prior to MPTP, could not restore dopamine in striatum but in contrast maintained a normal ratio of the reduced form to the oxidized form of coenzyme Q, suggesting an interaction of lipoic acid with energy metabolism which seems, however, not only to be due to an activation of pyruvate dehydrogenase.

Grammatopoulos TN, Ahmadi F, Jones SM, Fariss MW, Weyhenmeyer JA, Zawada WM. 2005. Anglotensin II protects cultured midbrain dopaminergic neurons against rotenone-induced cell death. Brain Res 1045(1-2):64-71. Abstract: In this study, we demonstrate that angiotensin II (Ang II) protects dopamine (DA) neurons from rotenone toxicity in vitro. Primary ventral mesencephalic (VM) cultures from E 15 rats were grown for 5 days and then cultured in the presence of the mitochondrial complex I inhibitor, rotenone. Acute exposure (20 h) to 20 nM rotenone reduced the number of tyrosine hydroxylase-positive (TH+) neurons by 50 6% when compared to untreated cultures. Pre-treatment of VM cultures with 100 nM Ang II decreased TH+ neuronal loss to 25 +/- 10% at the 20-nM rotenone

concentration. Ang II in the presence of the angiotensin type I receptor (AT(1)R) antagonist, losartan, was even more effective in protecting DA neurons showing a loss of only 13 +/- 4% at 20 nM rotenone. Conversely, the AT(2)R antagonist, PD123319, abolished the protective effects of Ang II. Furthermore, both the NMDA receptor antagonist, MK801, and the antioxidant, alpha-tocopheryl succinate (vitamin E analogue), prevented rotenone-induced toxicity. Here, we show that acute exposure of VM cultures to the pesticide rotenone leads to dopaminergic neuronal cell death and that angiotensin acting through the AT(2) receptor protects dopamine neurons from rotenone toxicity. (C) 2005 Elsevier B.V. All rights reserved.

Grandas F, Artieda J, Obeso JA. 1989. Clinical and CT scan findings in a case of cyanide intoxication. Mov Disord 4(2):188-93.
Abstract: A 39-year-old man showed a combination of severe parkinsonism and progressive dystonia following attempted suicide with sodium cyanide. Computed tomography (CT) scan showed bilateral lucencies in the putamen and external globus pallidus. The topography of lesions on CT scan closely correlated with the pathological findings described in a previous report of cyanide-induced parkinsonism. This is the first reported case of cyanide intoxication with delayed-onset dystonia.

Grant KA, Colombo G, Grant J, Rogawski MA. 1996. Dizocilpine-like discriminative stimulus effects of low-affinity uncompetitive NMDA antagonists. Neuropharmacology 35(12):1709-1719.
Abstract: The dizocilpine-like discriminative stimulus effects of a variety of channel blocking (uncompetitive) N-methyl-D-aspartate (NMDA) receptor antagonists were examined in rats trained to discriminate dizocilpine (0.17 mg/kg, i.p) from saline in a two-lever operant procedure. The dissociative anesthetic-type NMDA antagonists dizocilpine (ED(50) 0.05 mg/kg), phencyclidine (ED(50) 3.4 mg/kg) and ketamine (ED(50) 14 mg/kg) showed complete substitution without producing significant decreases in response rates, whereas dexoxadrol (ED(50) 4.3 mg/kg) also produced complete substitution with a concomitant decrease (35%) in response rate. Similarly, the low-affinity antagonist memantine resulted in complete substitution (ED(50) 9.7 mg/kg) at doses that significantly reduced (68%) the response rate. All other low-affinity antagonists resulted in either partial or no substitution for the discriminative stimulus effects of dizocilpine at doses that significantly decreased average response rates. These include (ED(50) values in parentheses) remacemide (29 mg/kg), the remacemide metabolite 1,2-diphenyl-2-propylamine (ARL 12495) (14 mg/kg), phencylcyclopentylamine (25 mg/kg), dextromethorphan (46 mg/kg), (+/-)-5-aminocarbonyl-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5,10-imi ne (ADCI; no substitution) and levoxadrol (no substitution). We conclude that low-affinity uncompetitive NMDA antagonists have discriminative stimulus properties distinct from dissociative anesthetic-type uncompetitive NMDA antagonists. The lowest-affinity antagonists show virtually no substitution for dizocilpine, whereas the relatively more potent low-affinity antagonists (such as memantine) exhibit greater substitution, but complete substitution is obtained only at rate-reducing doses. (C) 1997

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Grassi L, Biancosino B, Marmai L, Righi R. 2004. Effect of reboxetine on major depressive disorder in breast cancer patients: An open-label study. J Clin Psychiatry 65(4):515-520.
Abstract: Background: Depression is a common disorder in cancer patients, and it is associated with reduced quality of life, abnormal illness behavior, pain, and suicide risk. A few studies have investigated the effects of tricyclic antidepressants and serotonin reuptake inhibitors in cancer patients. No data are available regarding the use of reboxetine, a norepinephrine reuptake inhibitor that has been shown to be safe (e.g., absence of clinically significant drug-drug interactions and cytochrome P450 metabolism) and effective in the treatment of depressed patients, including those with medical illness (e.g., Parkinson's disease, human immunodeficiency virus infection). Method: The effects of reboxetine were investigated in 20 breast cancer patients with a DSM-IV diagnosis of major depressive disorder in an open, prospective 8-week trial. Severity of depression was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D). Psychiatric symptoms (Brief Symptom Inventory [BSI]), styles of coping with cancer (Mini-Mental Adjustment to Cancer [Mini-MAC]), quality of life (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 [EORTC-QLQ-C30]), and Clinical Global Impressions scale scores were also monitored. Results: At 8 weeks, a significant ($p < .01$) reduction was observed in HAM-D scores, several BSI dimension scores, and Mini-MAC hopelessness and anxious preoccupation scores. A significant ($p < .05$) improvement from baseline to endpoint was found on the EORTC-QLQ-C30 subfactors emotional, cognitive, dyspnea, steep, and global. Discontinuation was necessary in 1 subject because of hypomanic switch and in another because of side effects (tachycardia, tension). Seven patients experienced transient side effects (e.g., mild anxiety, insomnia, sweating). Conclusion: In this open trial, reboxetine appeared to be well tolerated and promising in reducing depressive symptoms and maladjusted coping styles and in improving scores on quality-of-life parameters.

Greenamyre JT, Betarbet R, Sherer T, Panov A . 2001. Response: Parkinson's disease, pesticides and mitochondrial dysfunction. Trends Neurosci 24(5): 247.

Greenamyre JT, Betarbet R, Sherer TB. 2003. The rotenone model of Parkinson's disease: genes, environment and mitochondria. Parkinsonism & Related Disorders 9:S59-S64.
Abstract: Parkinson's disease (PD) is occasionally caused by single gene mutations or by single toxic exposures, but most cases of PD are probably caused by some combination of genetic susceptibility and environmental exposure. Using rotenone as a prototype for an environmental toxicant, we argue here that genetic and environmental causes of PD converge on common pathogenic mechanisms. If so, protective strategies devised for one type of PD may be broadly useful for other forms of the disease. (C)

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Greenamyre JT, Higgins DS, Eller RV. 1992. Quantitative autoradiography of dihydrorotenone binding to complex-i of the electron-transport chain. J Neurochem 59(2):746-749.
Abstract: Defective complex I activity has been linked to Parkinson's disease and Huntington's disease, but little is known of the regional distribution of this enzyme in the brain. We have developed a quantitative autoradiographic assay using [H-3]dihydrorotenone ([3]DHR) to label and localize complex I in brain tissue sections. Binding was specific and saturable and in the cerebellar molecular layer had a K(D) of 11.5 +/- 1.3 nM and a B(max) of 11.0 +/- 0.4 nCi/mg of tissue. Unlabeled rotenone and 1-methyl-4-phenylpyridinium ion competed effectively for DHR binding sites. Binding was markedly enhanced by 100-mu-M NADH. The distribution of complex I in brain, as revealed by DHR autoradiography, is unique but somewhat similar to that of cytochrome oxidase (complex IV). This assay may provide new insight into the roles of complex I in brain function and neurodegeneration.

Greenamyre JT, Mackenzie G, Peng TI, Stephans SE. 1999. Mitochondrial Dysfunction in Parkinson's Disease66. p 85-97. Mitochondria and Cell Death: Biochemical Society Symposium.
Abstract: The cause of Parkinson's disease (PD) is unknown, but reduced activity of complex I of the electron-transport chain has been implicated in the pathogenesis of both mitochondrial permability transition pore-induced Parkinsonism and idiopathic PD. We developed a novel model of PD in which chronic, systemic infusion of rotenone, a complex-I inhibitor, selectively kills dopaminergic nerve terminals and causes retrograde degeneration of substantia nigra neurons over a period of months. The distribution of dopaminergic pathology replicates that seen in PD, and the slow time course of neurodegeneration mimics PD more accurately than current models. Our model should enhance our understanding of neurodegeneration in PD. Metabolic impairment depletes ATP, depresses Na+/K+-ATPase activity, and causes graded neuronal depolarization. This relieves the voltage-dependent Mg2+ block of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, which is highly permeable to Ca2+ Consequently, innocuous levels of glutamate become lethal via secondary excitotoxicity. Mitochondrial impairment also disrupts cellular Ca2+ homoeostasis. Moreover, the facilitation of NMDA-receptor function leads to further mitochondrial dysfunction. To a large part, this occurs because Ca2+ entering neurons through NMDA receptors has 'privileged' access to mitochondria, where it causes free-radical production and mitochondrial depolarization. Thus there may be a feed-forward cycle wherein mitochondrial dysfunction causes NMDA-receptor activation, which leads to further mitochondrial impairment. In this scenario, NMDA-receptor antagonists may be neuroprotective.

Greenamyre JT, Sherer TB, Betarbet R, Panov AV. 2001. Complex I and Parkinson's disease. Iubmb Life 52(3-5):135-141.
Abstract: Complex I of the mammalian electron transfer chain is composed

of at least 43 protein subunits, of which 7 are encoded by mtDNA. It catalyzes the transfer of electrons from NADH to ubiquinone and translocates protons from the mitochondrial matrix to the intermembrane space. It may also play direct roles in the mitochondrial permeability transition and in cell death pathways. Despite the limitations of current complex I assays, biochemical studies have suggested the presence of a mild, systemic defect of complex I in Parkinson's disease (PD). Recent experimental work has modeled this abnormality using rotenone to systemically inhibit complex I. Chronic rotenone exposure accurately recapitulated the pathological, biochemical, and behavioral features of PD. Thus, relatively subtle complex I abnormalities-either genetic or acquired-may be central to the pathogenesis of PD.

Greenlee AR, Burmester JK, Hiner BC. 2002. Pesticide exposure, host susceptibility factors and risk of Parkinson's disease: an introduction to a work in progress. WMJ 101(5):20-4.

Greer CL, Grygoruk A, Patton DE, Ley B, Romero-Calderon R, Chang HY, Houshyar R, Bainton RJ, Diantonio A, Krantz DE. 2005. A splice variant of the Drosophila vesicular monoamine transporter contains a conserved trafficking domain and functions in the storage of dopamine, serotonin, and octopamine. J Neurobiol 64(3):239-258.
Abstract: Vesicular monoamine transporters (VMATs) mediate the transport of dopamine (DA), serotonin (5HT), and other monoamines into secretory vesicles. The regulation of mammalian VMAT and the related vesicular acetylcholine transporter (VAChT) has been proposed to involve membrane trafficking, but the mechanisms remain unclear. To facilitate a genetic analysis of vesicular transporter function and regulation, we have cloned the Drosophila homolog of the vesicular monoamine transporter (dVMAT). We identify two mRNA splice variants (DVMAT-A and B) that differ at their C-terminus, the domain responsible for endocytosis of mammalian VMAT and VAChT. DVMAT-A contains trafficking motifs conserved in mammals but not C. elegans, and internalization assays indicate that the DVMAT-A C-terminus is involved in endocytosis. DVMAT-B contains a divergent C-terminal domain and is less efficiently internalized from the cell surface. Using in vitro transport assays, we show that DVMAT-A recognizes DA, 5HT, octopamine, tyramine, and histamine as substrates, and similar to mammalian VMAT homologs, is inhibited by the drug reserpine and the environmental toxins 2,2,4,5,6-penta-chlorobiphenyl and heptachlor. We have developed a specific antiserum to DVMAT-A, and find that it localizes to dopaminergic and serotonergic neurons as well as octopa-minergic, type 11 terminals at the neuromuscular junction. Surprisingly, DVMAT-A is co-expressed at type 11 terminals with the Drosophila vesicular glutamate transporter. Our data suggest that DVMAT-A functions as a vesicular transporter for DA, 5HT, and octopamine in vivo, and will provide a powerful invertebrate model for the study of transporter trafficking and regulation. (c) 2005 Wiley Periodicals, Inc.

Gu M, Irvani M, Cooper JM, King D, Jenner P, Schapira AHV. 2004. Pramipexole protects against apoptotic cell death by non-dopaminergic mechanisms. J

Neurochem 91(5):1075-1081.
Abstract: We have investigated the ability of pramipexole, a dopamine agonist used in the symptomatic treatment of Parkinson's disease (PD), to protect against cell death induced by 1-methyl-4-phenylpyridinium (MPP+) and rotenone in dopaminergic and non-dopaminergic cells. Pre-incubation with either the active (-)- or inactive (+)-enantiomer forms of pramipexole (10 muM) decreased cell death in response to MPP+ and rotenone in dopaminergic SHSY-5Y cells and in non-dopaminergic JK cells. The protective effect was not prevented by dopamine receptor blockade using sulpiride or clozapine. Protection occurred at concentrations at which pramipexole did not demonstrate antioxidant activity, as shown by the failure to maintain aconitase activity. However, pramipexole reduced caspase-3 activation, decreased the release of cytochrome c and prevented the fall in the mitochondrial membrane potential induced by MPP + and rotenone. This suggests that pramipexole has anti-apoptotic actions. The results extend the evidence for the neuroprotective effects of pramipexole and indicate that this is not dependent on dopamine receptor occupation or antioxidant activity. Further evaluation is required to determine whether the neuroprotective action of pramipexole is translated to a disease-modifying effect in PD patients.

Guilloteau D, Chalon S. 2005. PET and SPECT exploration of central monoaminergic transporters for the development of new drugs and treatments in brain disorders. Curr Pharm Des 11(25):3237-3245.
Abstract: Membrane and vesicular monoaminergic transporters, responsible for the homeostasis of neurotransmitter pools at nerve endings, are very involved in the physiology and diseases of central nervous system. Recent progresses of cerebral molecular imaging using SPECT and PET methods allow the extend of in vivo exploration of these transporters. For this aim, an increasing number of radiopharmaceuticals labelled with [I-123], [(99)mTc], [C-11] or [F-18] have been developed such as cocaine derivatives for the DAT, compounds from the diphenyl sulfide family for the SERT, and dihydrotetrabenazine derivatives for the VMAT(2). These functional imaging methods can be very useful in several neurological and psychiatric disorders which involve the monoaminergic neurotransmission systems such as Parkinson's disease, ADHD, depression and autism. For example, the DAT is a specific index of the density of dopaminergic endings which progressively degenerate in Parkinson's disease. In vivo exploration of this transporter can therefore be a relevant way (i) to realize an early detection of the loss of dopaminergic neurons, (ii) to assess the progression of the disease, (iii) to validate and improve the efficacy of new therapeutic strategies such as neuroprotection and neuroreparation. In all, the extend of in vivo exploration of monoamine transporters will allow great progress for (1) knowledge of physiopatho logical mechanisms of brain disorders, (2) early diagnosis of cerebral dysfunctions, allowing early use of new therapies, (3) selection of homogenous classes of subjects for therapeutic assays, (4) objectiveness of drug-molecular target interaction, (5) follow-up of disease evolution and treatment.

Hageman G, Van Der Hoek J, Van Hout M, Van Der Laan G, Steur EJ, De Bruin W, Herholz K. 1999. Parkinsonism, pyramidal signs, polyneuropathy, and cognitive decline after long-term occupational solvent exposure. J Neurol 246(3):198-206.
Abstract: It is well known that exposure to manganese, solvents, or carbon monoxide in an occupational setting may lead to central nervous system damage and parkinsonism. The most important solvents in this respect are methanol, toluene, carbon disulfide, and n-hexane, We describe three patients who had been exposed to various solvents for more than 20 years (25, 34, and 46 years). They presented with parkinsonism, pyramidal signs, mild cognitive decline, and unresponsiveness to levodopa, Two patients had a predominantly axonal and sensory polyneuropathy of the lower legs with fasciculations in one of them. Parkinsonian features were progressive, even after the patients had stopped work. We present clinical data, neuropsychological findings, and results of brain computed tomography or magnetic resonance imaging, electroneuromyography, evoked potentials, single photon emission computed tomography, and positron-emission tomography. There is growing evidence that various organic solvents give rise to a parkinsonism syndrome with pyramidal features in susceptible individuals.

Hanna PA, Jankovic J, Kirkpatrick JB. 1999. Multiple system atrophy - The putative causative role of environmental toxins. Arch Neurol 56(1):90-94.
Abstract: Background: Whereas a number of studies have investigated the putative role of environmental toxins in the pathogenesis of idiopathic Parkinson disease, the possibility of such a role in multiple system atrophy has received little attention. Design and Setting: Review of records of patients examined in the Parkinson's Disease Center and Movement Disorder Clinic, Baylor College of Medicine, Houston, Tex, from July 1, 1977, to February 4, 1998. Patients: We reviewed 100 consecutive medical records of patients who satisfied the diagnostic criteria for multiple system atrophy formulated by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Intervention: The type and amount of toxin exposure were verified by history and examination of records whenever er possible. Severity of parkinsonism was assessed by clinical rating scales. Main Outcome Measure: Development of multiple system atrophy after environmental toxin exposure. Results: Eleven patients had a notable history of heavy exposure to environmental toxins. One patient with multiple system atrophy confirmed by postmortem evaluation was exposed to high concentrations of malathion, diazinon, and formaldehyde, while the other patients with multiple system atrophy had well-documented high exposures to agents including n-hexsane, benzene, methyl isobutyl ketone, and pesticides. The case studied pathologically demonstrated extensive advanced glial changes, including glial cytoplasmic inclusions in deep cerebellar white matter, brainstem, cortex (superior frontal, insula) and putamen, with notable cell loss and depigmentation of the substantia nigra and locus ceruleus. Conclusion: While many studies report a possible role of environmental toxins in Parkinson disease, such a role is even more

likely in multiple system atrophy, as this is a sporadic disease.

Hara S, Mukai T, Kurosaki K, Kuriiwa F, Yanase T, Kano S, Endo T. 2001. No parallel relationship between nitric oxide production and wet dog shakes susceptible to nitric oxide synthase inhibitors following systemic administration of paraquat in rats. Arch Toxicol 74(12):775-782.
Abstract: Shaking behavior, so-called wet dog shakes (WDS), in rats is characteristic behavior indicating morphine abstinence in morphine-dependence and central excitation in relation to seizures elicited by chemicals or electrical stimulation. We have found that paraquat (PQ), a nonselective herbicide, administered systemically to rats induces WDS in a dose-dependent manner. PQ-induced WDS are suppressed by nitric oxide (NO) synthase (NOS) inhibitors, but this suppression is not reversed by an NO precursor, L-arginine (L-Arg). The present study was performed to determine whether the NO system is associated with PQ-induced WDS in rats. A time-course study on the frequency of WDS for each 30-min period up to 120 min after PQ administration (70 mg/kg, s.c.) revealed that significant induction of WDS occurred during the first and second 30-min periods, that is within 60 min of PQ administration. A nonselective NOS inhibitor, N-omega-nitro-L-arginine (L-NA; 30 mg/kg, i.p.), reduced the frequency of the PQ-induced WDS during both of these periods, but the reduced frequency was not reversed by L-Arg (500 mg/kg, i.p.) in either period. Significant induction of WDS occurred when PQ (50 nmol) was administered directly into the ventral or dorsal hippocampus, but not when administered into the amygdala or the caudate putamen, indicating that the hippocampus plays an important role in PQ-induced WDS. The WDS after the administration of PQ into the dorsal hippocampus was significantly suppressed by pretreatment with L-NA (30 mg/kg, i.p.). The extracellular levels of nitrite (NO2-) and nitrate (NO3-), the oxidative products of NO, in the dorsal hippocampus determined by in vivo microdialysis, were stimulated after systemic PQ administration (70 mg/kg, s.c.) in urethane-anesthetized rats. The increases in extracellular NO2-, and NO3- were inhibited by L-NA (30 mg/kg, i.p.), and this inhibition was partly reversed by L-Arg (500 mg/kg, i.p.). The increases in extracellular NO2- and NO3- in the dorsal hippocampus appeared 60 min after PQ administration, when the WDS had occurred and disappeared. These findings suggest that NO production in the hippocampus plays a minor role in PQ-induced WDS in rats and that the suppression of PQ-induced WDS by NOS inhibitors might be mediated though complex mechanisms in the brain.

Harris EC, Barraclough BM. 1994. Suicide as an outcome for medical disorders. Medicine (Baltimore) 73(6):281-296.

Hart TB. 1987. Parkinsons-disease and pesticides. Lancet 1(8523):38.

Hartley A, Stone JM, Heron C, Cooper JM, Schapira AHV. 1994. Complex-i inhibitors induce dose-dependent apoptosis in pc12 cells - relevance to parkinsons-disease. J Neurochem 63(5):1987-1990.
Abstract: The mode of cell death in Parkinson's disease (PD) substantia nigra is uncertain. However, evidence is accumulating that certain of the

biochemical abnormalities present in PD nigra at the time of death may precipitate apoptosis. We have investigated the mode of death induced by complex I inhibition of dopaminergic cell cultures, and our results suggest that both 1-methyl-4-phenylpyridinium and rotenone cause apoptosis at low concentrations and necrosis at high concentrations. This dose-dependent shift in the mode of cell death induced by these mitochondrial toxins may have important implications for the mechanism of neuronal cell death in PD.

Hasegawa E, Kang D, Sakamoto K, Mitsumoto A, Nagano T, Minakami S, Takeshige K. 1997. A dual effect of 1-methyl-4-phenylpyridinium (MPP(+))-analogs on the respiratory chain of bovine heart mitochondria. Arch Biochem Biophys 337(1):69-74.
Abstract: We examined effects of several compounds, structurally related to 1-methyl-4-phenylpyridinium (MPP(+)), on the NADH-dependent respiration of bovine heart submitochondrial particles, 1-Methyl-4-(3'-trimethylammoniophenyl)pyridinium (analog 8) as well as MPP(+) completely inhibited O-2 consumption, reduction of ubiquinone-10, and reduction of cytochrome b in a dose-dependent manner. The production of superoxide (O-2(-)) induced by MPP(+) or analog 8 was to the same extent as that by rotenone, an inhibitor of complex I of the mitochondrial respiratory chain. Rotenone had no additive effect on the maximal production of O-2(-) induced by MPP(+) or analog 8, suggesting that the production was mediated by the same way as rotenone, 1-Methyl-4-(4'-nitrophenyl) pyridinium (analog 1) induced about 20-fold more production of O-2(-) than MPP(+) and the production was additively increased by rotenone, Analog 1 only partially inhibited rotenone-sensitive O-2 consumption, Paraquat induced the production of O-2(-) as much as analog 1, Paraquat, however, did not inhibit rotenone sensitive O-2 consumption or reduction of cytochrome b, These results suggest that MPP(+) and its analogs interact with the mitochondrial respiratory chain at two sites, the substrate side of the rotenone-binding site and the rotenone-binding site. The analogs may be reduced to produce O-2(-) at the former site and inhibit the respiratory chain at the latter site. (C) 1997 Academic Press, Inc.

Hashimoto M, Bar-on P, Ho G, Takenouchi T, Rockenstein E, Crews L, Masliah E. 2004. beta-synuclein regulates Akt activity in neuronal cells - A possible mechanism for neuroprotection in Parkinson's disease. J Biol Chem 279 (22):23622-23629.
Abstract: Recent studies have shown that the neurodegenerative process in disorders with Lewy body formation, such as Parkinson's disease and dementia with Lewy bodies, is associated with alpha-synuclein accumulation and that beta-synuclein might protect the central nervous system from the neurotoxic effects of alpha-synuclein. However, the mechanisms are unclear. The main objective of the present study was to investigate the potential involvement of the serine threonine kinase Akt ( also known as protein kinase B) signaling pathway in the mechanisms of beta-synuclein neuroprotection. For this purpose, Akt activity and cell survival were analyzed in synuclein-transfected B103 neuroblastoma cells

and primary cortical neurons. beta-Synuclein transfection resulted in increased Akt activity and conferred protection from the neurotoxic effects of rotenone. Down-regulation of Akt expression resulted in an increased susceptibility to rotenone toxicity, whereas transfection with a lentiviral vector encoding for beta-synuclein was protective. The effects of beta-synuclein on the Akt pathway appear to be by direct interaction between these molecules and were independent of upstream signaling molecules. Taken together, these results indicate that the mechanisms of beta-synuclein neuroprotection might involve direct interactions between beta-synuclein and Akt and suggest that this signaling pathway could be a potential therapeutic target for neurological conditions associated with parkinsonism and alpha-synuclein aggregation.

Haskel Y, Udassin R, Chevion M. 1991. Mechanistic aspects of 1-methyl-4-phenyl pyridinium iodide toxicity in escherichia-coli - the role of oxygen and hydrogen-peroxide. Isr J Med Sci 27(4):207-212.
Abstract: 1-Methyl-4-phenyl pyridinium iodide (MPP+) and paraquat (PQ +2) are two structurally analogous and highly toxic pyridinium compounds. The mechanism of PQ+2 toxicity is best understood in the bacterial model system. While numerous studies in a variety of systems have indicated the causative role of free radicals and other oxygen-derived active species in PQ+2 toxicity, this question is yet unresolved in the case of MPP+. In this study we have used the Escherichia coli model and demonstrated that MPP+ is toxic to bacterial cells in dose- and time-dependent modes. Additionally, it is shown that only in the presence of molecular oxygen did bacterial inactivation occur. This requirement for oxygen can be circumvented by adventitious H2O2. The protective effects of the chemical scavenger - mannitol - and of histidine are presented. These results are in complete accord with a free radical mechanism for MPP+ toxicity.

Hathway DE. 2000. Toxic action/toxicity. Biological Reviews 75(1):95-127.
Abstract: Some six or so physiological systems, essential to normal mammalian life, are involved in poisoning; an intoxication that causes severe injury to any one of them could be life threatening. Reversible chemical reactions showing Scatchard-type binding are exemplified by CO, CN- and cyclodiene neurotoxin insecticide intoxications, and by antigen-antibody complex: formation. Haemoglobin (Hb:) molecular biology accounts for the allosteric co-operativity and other characteristics of CO poisoning, CN- acts as a powerful cytochrome oxidase inhibitor, and antigen binding in a deep antibody cleft between two domains equipped with epitopes for antigen-binding groups explains hapten-specific immune reactions. Covalent chemical reactions with second-order (S(N)2) kinetics characterize Hg and Cd poisonings, the reactions of organophosphates and phosphonates with acetylcholinesterase and neurotoxic esterase and the reaction sequence whereby Paraquat accepts electrons and generates superoxide under aerobic conditions. Indirect carcinogens require cytochrome P450 activation to form DNA adducts in target-organ DNA and cause cancer, but a battery of detoxifying enzymes clustered with the P450 system must be overcome. Thus, S-metabolism competes ineffectively with target DNA for reactive vinyl chloride (VC) metabolites, epoxide

hydrolase is important to the metabolism and carcinogenicity of aflatoxins and polycyclic aromatic hydrocarbons (benzo[a]pyrene, etc.), and the non-toxic 2-naphthylhydroxylamine N-glucuronide acts as a transport form in 2-naphthylamine bladder cancer. VC liver-cancer pathogenesis is explicable in terms of the presence of the glutathione S-transferase detoxifying system in hepatocytes and its absence from the fibroblastic elements, and of the VC concentrations reaching the liver by different administrative routes. In VC carcinogenicity, chemical reactions give imidazo-cyclization products with nucleoside residues of target DNA, and in benzene leukaemia, Z,Z-muconaldehyde forms cyclic products containing a pyrrole residue linked to purine. Increased HbCO concentrations reduce the O-2-carrying capacity of the blood, and the changed shape of the O-2-Hb dissociation curve parallels disturbance in O-2 unloading. CN- acts on electron transport and paralyses respiration. In telodrin poisoning, preconvulsive glutamine formation abstracts tricarboxylic acid intermediates incommensurately with normal cerebral respiration. Antigen-antibody complexing depletes the antibody titre, available against infection. At high doses of Cd, Cd-thionein filtered through the kidneys is reabsorbed and tubular lesions produced. Some organophosphate insecticides promote irreversible acetylcholinesterase phosphorylation and blockade nerve function, and others react with neurotoxic esterase to cause delayed neuropathy. The evidence far Paraquat pulmonary poisoning suggests a radical mechanism involving three interrelated cyclic reaction stages. The action of N- and O-6 (O substituent in 6-position of the purine) demethylases explains deletion mechanisms for DNA-alkyl adducts. DNA-directed synthesis in the presence of ultimate carcinogens provides for an estimation of misincorporations, which implicate the same transversions as those found by direct mutagenicity testing. Chemical carcinogens recognize tissue-sensitive cells and modify their heritable genetic complement. Oncoproteins encoded by activated oncogenes signal the transformation of normal cells into cancer cells. The importance of the H-ras oncogene and p53 tumour-suppressor gene is stressed. Antidotal action is analysed; for example, parenteral glutamine administration to telodrin-intoxicated rats restores the depleted cerebral glutamate level and prevents seizures. Glutamate acts as anticonvulsant in petit mal epilepsy. In general, therefore, the reaction of the toxicant-related substance with the relevant target-tissue macromolecule accounts for the biochemical/biological events at a cellular level and also the symptoms in the living mammal. This mechanism is analogous to mechanisms for diseases such as arthritis and Parkinsonism.

He Y, Imam SZ, Dong ZJ, Jankovic J, Ali SF, Appel SH, Le WD. 2003. Role of nitric oxide in rotenone-induced nigro-striatal injury. J Neurochem 86(6): 1338-1345.

Abstract: Rotenone, a widely used pesticide, causes a syndrome in rats that mimics, both behaviorally and pathologically, the symptoms of Parkinson's disease. The present study evaluated the role of nitric oxide in rotenone-induced nigro-striatal injury. After administration of rotenone in rats for 40 days, there was a moderate but significant injury of the nigro-

striatal pathway indicated by a 47% decrease in striatal dopamine levels and a 28% loss of substantia nigra tyrosine hydroxylase-immunopositive neurons. Furthermore, a significant (37%) increase in the number of cells positive for nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) in the striatum was observed, accompanied by a 83% increase in nitric oxide synthase (NOS) activity and a significant increase in the production of 3-nitrotyrosine (3-NT). There was a significant increase (45%) in the optical density of NADPH-d staining and an increase (72%) in NOS activity in the substantia nigra. Moreover, administration of the neuronal NOS inhibitor 7-nitroindazole significantly attenuated the increased NOS activity and 3-NT production, and provided significant protection against rotenone-induced nigro-striatal injury. Our data suggest that chronic rotenone administration can lead to significant injury to the nigro-striatal system, mediated by increased generation of nitric oxide.

Heier RF, Moon MW, Stolle WT, Easter JA, Hsi RSP. 1996. An asymmetric synthesis of (R)-5-(methylamino)-5,6-dihydro-4H-imidazo-[4,5,1-ij] quinolin-2(1H)-one (1) and its [2-C-14]- and [6,7-H-3(2)]-labeled forms. Journal of Labelled Compounds & Radiopharmaceuticals 38(12):1087-1098. Abstract: (R)-5-(Methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij] quinolin-2 (1H)-one (1) is a dopamine agonist which shows selectivity for the D2 receptor subtype, and is of interest as a potential drug for the treatment of Parkinson's disease. An asymmetric epoxidation approach has been used to prepare 1 in eleven steps (15% overall yield) from 8-nitroquinoline. An advanced intermediate in this synthesis, tert-butyl (R)-methyl(8-amino-1,2,3,4-tetrahydro-3-quinolinyl)carbamate (10), has been reacted with [C-14]phosgene to provide a two-step synthesis of 1 labeled with carbon-14 at the C-2 position (236 mu Ci/mg). Bromination of 1 gave the dibromo analogue 12b which was reduced in the presence of tritium gas to give 1 labeled with tritium at the C-6 and C-7 positions (28.5 Ci/mmol). In addition to providing syntheses for labeled forms of the drug which are useful in drug disposition and receptor binding studies, this approach also provides a convenient synthesis for the unlabeled form of drug.

Helmuth L. 2000. Neuroscience - Pesticide causes Parkinson's in rats. Science 290(5494):1068.

Hensley K, Pye QN, Maidt ML, Stewart CA, Robinson KA, Jaffrey F, Floyd RA. 1998. Interaction of alpha-phenyl-N-tert-butyl nitrone and alternative electron acceptors with complex I indicates a substrate reduction site upstream from the rotenone binding site. J Neurochem 71(6):2549-2557. Abstract: Mitochondrial complexes I, II, and III were studied in isolated brain mitochondrial preparations with the goal of determining their relative abilities to reduce Ca to hydrogen peroxide (H2O1) or to reduce the alternative electron accepters nitroblue tetrazolium (NBT) and diphenyliodonium (DPI). Complex I and II stimulation caused H2O2 formation and reduced NET and DPI as indicated by dichlorodihydrofluorescein oxidation, nitro-formazan precipitation, and DPI-mediated enzyme inactivation. The O-2 consumption rate was more rapid under complex II (succinate) stimulation than under complex I (NADH)

stimulation. In contrast, H2O2 generation and NET and DPI reduction kinetics were favored by NADH addition but were virtually unobservable during succinate-linked respiration. NADH oxidation was strongly suppressed by rotenone, but NADH-coupled H2O2 flux was accelerated by rotenone. alpha-Phenyl-N-tert-butyl nitrone (PBN), a compound documented to inhibit oxidative stress in models of stroke, sepsis, and parkinsonism, partially inhibited complex I-stimulated H2O2 flux and NET reduction and also protected complex I from DPI-mediated inactivation while trapping the phenyl radical product of DPI reduction. The results suggest that complex I may be the principal source of brain mitochondrial H2O2 synthesis, possessing an "electron leak" site upstream from the rotenone binding site (i,e., on the NADH side of the enzyme). The inhibition of H2O2 production by PEN suggests a novel explanation for the broad-spectrum antioxidant and antiinflammatory activity of this nitrone spin trap.

Herishanu YO, Kordysh E, Goldsmith JR. 1998. A case-referent study of extrapyramidal signs (preparkinsonism) in rural communities of Israel. Can J Neurol Sci 25(2):127-133.
Abstract: Background: In previous studies we reported an increased prevalence of Parkinson's disease in several kibbutzim of Southern Israel (cluster kibbutzim). Subsequent studies revealed a significant prevalence of subjects presenting extrapyramidal signs (preparkinsonism) in the same kibbutzim. On follow-up worsening of these signs was observed in some of the older subjects, some of them actually being diagnosed as suffering from 1-Dopa responsive Parkinson's disease. The current study was designed to evaluate possible etiologic factors for the development of preparkinsonism. Methods: 317 subjects over the age of 40, living in five kibbutzim were examined and interviewed. 95 subjects presenting extrapyramidal signs were compared with 95 control subjects. They were matched for age, sex and length of residence in the kibbutz. Odds ratios were computed to identify exposure variables for logistic regression analyses. Detectors for carbamates and organic phosphates were applied at different sites of these kibbutzim. Results: The severity and frequency of the extrapyramidal signs were higher in the older age groups, more in the "cluster", than in other kibbutzim. A very strong association was found between field crop work exposure, particularly cotton, and preparkinsonism ($p = 0.0007$) and a slightly weaker association for landscape work. The detectors picked up abundant pesticide traces (carbamates and organic phosphates) in the residential areas fairly distant from sites of aerial spray. Conclusions: We assume a chronic passive exposure of the residents in these kibbutzim to pesticides, in addition to any occupational exposures.

Herishanu YO, Medvedovski M, Goldsmith JR, Kordysh E. 2001. A case-control study of Parkinson's disease in urban population of southern Israel. Can J Neurol Sci 28(2):144-147.
Abstract: Background: In recent years, an increased prevalence of Parkinson's disease (PD) in southern Israel was observed. The aim of this study was to determine which exposures are associated with PD in the urban population of this region. Methods: Ninety-three PD patients living in

towns were compared to 93 age and sex matched controls. A previously validated questionnaire, including demographic data, education, data on exposures, previous diseases, family history and habits, was administered. Results: In multivariate logistic regression analysis, it was found that history of work in construction sites was the strongest predictor of PD risk, followed by exposure to pesticides, in contrast, there was a negative association with smoking and history of mechanical factory employment. When the same statistical analysis was limited to association of PD with smoking, pesticides and construction work, the latter was found to be the strongest risk factor. Conclusion: The risk factors for PD in this population are work on a construction site and exposure to pesticides.

Hertzman C, Wiens M, Bowering D, Snow B, Calne D. 1990. Parkinson's disease: a case-control study of occupational and environmental risk factors. Am J Ind Med 17(3):349-55.
Abstract: We compared personal histories of 57 cases and 122 age-matched controls to identify possible environmental determinants of Parkinson's disease (PD). Odds ratios (OR) adjusted for sex, age, and smoking were computed using stepwise logistic regression. We found a statistically significant increased risk for working in orchards (OR = 3.69, p = 0.012, 95% CI = 1.34, 10.27) and a marginally significant increased risk associated with working in planer mills (OR = 4.11, p = 0.065, 95% CI = 0.91, 18.50). A Fisher's exact test of the association between PD development and (1) paraquat contact, and (2) postural tremor gave statistically significant probability estimates of 0.01 and 0.03, respectively. The relative risk of PD decreased with smoking, an inverse relationship supported by many studies.

Hertzman C, Wiens M, Snow B, Kelly S, Calne D. 1994. A case-control study of parkinsons-disease in a horticultural region of british-columbia. Mov Disord 9(1):69-75.
Abstract: We compared personal histories of 127 cases and 245 controls to identify possible environmental risk factors for idiopathic parkinsonism (IP). Of our controls, 121 had cardiac disease (CD) and 124 were randomly selected from electoral lists (voters). Using logistic regression and adjusting for sex and age, we ran separate analyses: IP versus CD and IP versus voters. A full occupational history was collected, as was known contact with all pesticides associated with the tree fruit sector of the agricultural industry. We found a significant association between IP and having had an occupation in which exposure through handling or directly contacting pesticides was probable, but no specific chemicals were associated with IP. We conclude that although occupations involving the use of agricultural chemicals may predispose to the development of IP, it seems likely that the pathogenesis is multifactorial rather than related to a specific agent.

Hider RC, Singh S, Porter JB. 1992. Iron chelating-agents with clinical potential. Proceedings of the Royal Society of Edinburgh Section B-Biological Sciences 99:137-168.
Abstract: Iron is a critically important metal for a wide variety of cellular

events. The element holds this central position by virtue of its facile redox chemistry and the high affinity of both redox states (iron II and iron III) for oxygen. These same properties also render iron toxic when levels exceed the normal binding capacity of the cell. As a result of this potential toxicity, selective iron chelators are finding an important role in the treatment of iron overload associated with many forms of thalassaemia. In addition, they appear to have potential in treating situations where a local increase in iron concentration causes an unfavourable pathology, for instance, in reperfused tissue (heart disease and stroke) and in Parkinsonian brain. There is also evidence that iron chelators may minimise the toxicity of paraquat and the side effects of bleomycin and doxorubicin. Non-haem iron enzymes can also be inhibited by iron chelators and consequently such enzymes as ribonucleotide reductase and lipoxygenase can be selectively inhibited. Such inhibitory action is being investigated for the treatment of malaria, neoplastic disease, psoriasis and asthma. Recent developments in these areas are discussed in the present overview.

Higgins DS, Greenamyre JT. 1996. [H-3]dihydrorotenone binding to NADH: Ubiquinone reductase (Complex I) of the electron transport chain: An autoradiographic study. J Neurosci 16(12):3807-3816.
Abstract: Abnormalities of mitochondrial energy metabolism may play a role in normal aging and certain neurodegenerative disorders. In this regard, complex I of the electron transport chain has received substantial attention, especially in Parkinson's disease, The conventional method for studying complex I has been quantitation of enzyme activity in homogenized tissue samples. To enhance the anatomic precision with which complex I can be examined, we developed an autoradiographic assay for the rotenone site of this enzyme. [H-3]dihydrorotenone ([H-3] DHR) binding is saturable (K-D = 15-55 nM) and specific, and Hill slopes of 1 suggest a single population of binding sites, Nicotinamide adenine dinucleotide (NADH) enhances binding 4- to 80-fold in different brain regions (EC(50) = 20-40 mu M) by increasing the density of recognition sites (B-max). Nicotinamide adenine dinucleotide phosphate also increases binding, but NAD(+) does not, In skeletal muscle, heart, and kidney, binding was less affected by NADH. [H-3]DHR binding is inhibited by rotenone (IC50 = 8-20 nM), meperidine (IC50 = 34-57 mu M), amobarbitol (IC50 = 375-425 mu M), and MPP(+) (IC50 = 4-5 mM), consistent with the potencies of these compounds in inhibiting complex I activity, Binding is heterogeneously distributed in brain with the density in gray matter structures varying more than 10-fold. Lesion studies suggest that a substantial portion of binding is associated with nerve terminals. [H-3]DHR autoradiography is the first quantitative method to examine complex I with a high degree of anatomic precision. This technique may help to clarify the potential role of complex I dysfunction in normal aging and disease.

Hinerfeld D, Traini MD, Weinberger RP, Cochran B, Doctrow SR, Harry J, Melov S. 2004. Endogenous mitochondrial oxidative stress: neurodegeneration, proteomic analysis, specific respiratory chain defects, and efficacious antioxidant therapy in superoxide dismutase 2 null mice. J Neurochem 88

(3):657-667.
Abstract: Oxidative stress and mitochondrial dysfunction have been linked to neurodegenerative disorders such as Parkinson's and Alzheimer's disease. However, it is not yet understood how endogenous mitochondrial oxidative stress may result in mitochondrial dysfunction. Most prior studies have tested oxidative stress paradigms in mitochondria through either chemical inhibition of specific components of the respiratory chain, or adding an exogenous insult such as hydrogen peroxide or paraquat to directly damage mitochondria. In contrast, mice that lack mitochondrial superoxide dismutase (SOD2 null mice) represent a model of endogenous oxidative stress. SOD2 null mice develop a severe neurological phenotype that includes behavioral defects, a severe spongiform encephalopathy, and a decrease in mitochondrial aconitase activity. We tested the hypothesis that specific components of the respiratory chain in the brain were differentially sensitive to mitochondrial oxidative stress, and whether such sensitivity would lead to neuronal cell death. We carried out proteomic differential display and examined the activities of respiratory chain complexes I, II, III, IV, V, and the tricarboxylic acid cycle enzymes alpha-ketoglutarate dehydrogenase and citrate synthase in SOD2 null mice in conjunction with efficacious antioxidant treatment and observed differential sensitivities of mitochondrial proteins to oxidative stress. In addition, we observed a striking pattern of neuronal cell death as a result of mitochondrial oxidative stress, and were able to significantly reduce the loss of neurons via antioxidant treatment.

Hirai M, Kitamura N, Hashimoto T, Nakai T, Mita T, Shirakawa O, Yamadori T, Amano T, Noguchi-Kuno SA, Tanaka C. 1988 Jul. [3H]GBR-12935 binding sites in human striatal membranes: binding characteristics and changes in parkinsonians and schizophrenics. Jpn J Pharmacol 47(3):237-43.
Abstract: The binding of the diphenyl-substituted piperazine derivative, [3H]GBR-12935, a selective dopamine uptake inhibitor, to the post-mortem human putamen was studied. Inhibition curves by dopamine uptake inhibitors suggested the existence of two populations of [3H]GBR-12935 binding sites: one is potently inhibited by mazindol and/or nomifensine, and the second binding site is benztropine- and/or GBR 12909-sensitive. In the human putamen, [3H]GBR-12935 labeled both these two distinct binding sites. The [3H]GBR-12935 binding displaced by mazindol was enriched in the mouse and rat striatum, but not in the cultured mouse neuroblastoma cell N1E-115. The mazindol-sensitive [3H]GBR-12935 binding site increased in the presence of sodium and markedly decreased in the putamen from parkinsonians (45% of controls). On the other hand, the [3H]GBR-12935 binding displaced by benztropine showed no sodium-dependent increase and was not decreased in the putamen from parkinsonians. In the putamen from schizophrenics, the [3H]GBR-12935 binding did not significantly change in the density, while that displaced by mazindol tended to increase. It is concluded that in the human putamen, [3H]GBR-12935 binds to two distinct sites. One site is partially sodium-dependent and appears to be associated with a high-affinity dopamine uptake system on dopaminergic nerve terminals. The second binding site

shows no sodium-dependency and may be associated with a nondopaminergic and/or extraneuronal DA uptake system.

Hirata Y, Nagatsu T. 2005. Rotenone and CCCP inhibit tyrosine hydroxylation in rat striatal tissue slices. Toxicology 216(1):9-14.
Abstract: Complex I inhibition has been implicated in the neurotoxicity of MPTP and rotenone, which reproduce a neurochernical and neuropathological feature of Parkinson's disease in experimental animals. Previous studies performed in rat striatal slices have shown that dopaminergic neurotoxins, MPTP and manganese, inhibit tyrosine hydroxylation, a rate-limiting step of dopamine biosynthesis. In this study, we examined the effect of mitochondrial toxins such as rotenone and carbonyl cyanide 3-chlorophenylhydrazone (CCCP) on tyrosine hydroxylation in rat striatal slices. Rotenone and CCCP inhibited DOPA formation with an accompanying decrease in ATP and increase in lactate of rat striatal slices during 1 h incubation. Furthermore, rotenone reduced dopamine (DA), dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) levels in PC 12 cells after 20 h incubation. These results suggest that tyrosine hydroxylation is inhibited in dopaminergic neurons soon after exposure to sub-micromolar concentrations of rotenone and CCCP, leading to dopamine depletion. (c) 2005 Elsevier Ireland Ltd. All rights reserved.

Hirata Y, Sugimura H, Takei H, Nagatsu T. 1986 Nov 12. The effects of pyridinium salts, structurally related compounds of 1-methyl-4-phenylpyridinium ion (MPP+), on tyrosine hydroxylation in rat striatal tissue slices. Brain Res 397(2):341-4.
Abstract: We had previously reported that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which produces Parkinson's disease in humans and animals, inhibited tyrosine hydroxylation, the rate-limiting step of dopamine synthesis, in striatal tissue slices after its conversion to 1-methyl-4-phenylpyridinium ion by monoamine oxidase. In this report, structurally related compounds of 1-methyl-4-phenylpyridinium ion (MPP+) were synthesized and tested for their ability to inhibit tyrosine hydroxylation in rat striatal tissue slices. The following pyridinium salts showed inhibitory effect on tyrosine hydroxylation: pyridinium salts that substituted the alkyl group for the methyl group of MPP+ (1-ethyl-, 1-propyl-, 1-isopropyl-4-phenylpyridinium ions); pyridinium salts that changed the position of the phenyl group (1-methyl-2-phenyl-, 1-methyl-3-phenylpyridinium ions); pyridinium salts that modified the phenyl ring at 4 position (1-methyl-4-tolylpyridinium ion, 1-methyl-4-(4'-methoxyphenyl) pyridinium ion); and N-methylisoquinolinium ion. In contrast, pyridinium salts in which the phenyl group was replaced with hydrogen, methyl or methoxycarbonyl group, paraquat (1,1'-dimethyl-4,4'-dipyridinium chloride, one of bipyridinium compounds and a widely used herbicide), and N-methylquinolinium ion, showed no inhibitory effect. Nomifensine, an inhibitor of dopamine uptake, prevented the inhibition caused by 1-methyl-2-phenylpyridinium ion. The result suggests that the effective pyridinium salts are taken up into dopaminergic neurons likewise MPP+ by the dopamine transport system and inhibit tyrosine hydroxylation in striatal tissue slices. N-methylisoquinolinium ion could be one of the candidates of

endogenous or environmental factors that produce Parkinson's disease.

Hirsch EC, Hoglinger G, Rousselet E, Breidert T, Parain K, Feger J, Ruberg M, Prigent A, Cohen-Salmon C, Launay JM. 2003. Animal models of Parkinson's disease in rodents induced by toxins: an update. Journal of Neural Transmission-Supplement (65):89-100.
Abstract: The development of animal models of Parkinson's disease is of great importance in order to test substitutive or neuroprotective strategies for Parkinson's disease. Such models should reproduce the main characteristics of the disease, such as a selective lesion of dopaminergic neurons that evolves over time and the presence of neuronal inclusions known as Lewy bodies. Optimally, such models should also reproduce the lesion of non-dopaminergic neurons observed in a great majority of patients with Parkinson's disease. From a behavioral point of view, a parkinsonian syndrome should be observed, ideally with akinesia, rigidity and rest tremor. These symptoms should be alleviated by dopamine replacement therapy, which may in turn lead to side effects such as dyskinesia. In this review, we analyze the main characteristics of experimental models of Parkinson's disease induced by neurotoxic compounds such as 6-hydroxydopamine, MPTP and rotenone. We show that, whereas MPTP and 6-hydroxydopamine induce a selective loss of catecholaminergic neurons that in most cases evolves over a short period of time, rotenone infusion by osmotic pumps can induce a chronically progressive degeneration of dopaminergic neurons and also of non-dopaminergic neurons in both the basal ganglia and the brainstem.

Hirsch EC, Hunot S, Hartmann A. 2005. Neuroinflammatory processes in Parkinson's disease. Parkinsonism & Related Disorders 11:S9-S15.
Abstract: In Parkinson's disease (PD), post-mortem examination reveals a loss of dopaminergic (DA) neurons in the substantia nigra (SN) associated with a massive astrogliosis and the presence of activated microglial cells. Similarly, microglial activation has also been reported to be associated with the loss of DA neurons in animal models of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, annonacine and lipopolysaccharide (LPS). Recent evidence suggests that the disease may progress even when the initial cause of neuronal degeneration has disappeared, raising the possibility that toxic substances released by glial cells could be involved in the propagation of neuronal degeneration. Inhibition of the glial reaction and the inflammatory processes may thus represent a therapeutic target to reduce neuronal degeneration in PD. (C) 2005 Elsevier Ltd. All rights reserved.

Hitri A, Hurd YL, Wyatt RJ, Deutsch SI. 1994. Molecular, functional and biochemical characteristics of the dopamine transporter - regional differences and clinical relevance. Clin Neuropharmacol 17(1):1-22.
Abstract: The carrier molecule that transports dopamine (DA) across the synaptic membrane is known as the dopamine transporter (DAT). Depending on the ionic conditions, DAT may function as a mediator of both the inward directed DA transport known as the ''reuptake'' and the outward directed DA transport known as the ''release.'' The functional significance

of DAT is in the regulation of DA neurotransmission by terminating the action of DA in the synapse via reuptake. With use of DAT binding as a presynaptic marker to measure altered DA innervation, abnormalities of the DAT binding have been demonstrated in idiopathic Parkinson's disease, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity, and progressive supranuclear palsy. Moreover, the identification of DAT as the neuronal element that mediates the addictive properties of cocaine highlights its significance in cocaine addiction. Cocaine binding in the brain is heterogeneous, and there is an uneven distribution of the high- and low-affinity binding sites across the anatomical regions. Regional differences in ligand binding are observed by using both [H-3]cocaine and the diphenyl-substituted piperazine derivatives known as the ''GBR series'' of ligands. The identification of compounds that inhibit the binding of cocaine without affecting DA uptake could potentially lead to development of medications for cocaine abuse. Furthermore, clarification of the various binding domains that may be relevant to transporter function in human neuropsychiatric disorders may lead to the development of new medications for schizophrenia, Tourette's disease, and drug addiction.

Ho SC, Woo J, Lee CM. 1989 Oct. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology 39(10):1314-8.
Abstract: In our cross-sectional survey of the residents of homes for the elderly in 2 Hong Kong districts--Shatin and Tai Po--we found that 3.4% of the subjects had Parkinson's disease (PD). There was no sex difference in the disease rate. We also conducted a case-control study to determine the associated factors of PD. We found that subjects with residence of long duration in rural areas, with engagement in farming, with previous use of herbicides and pesticides, and with habitual consumption of raw vegetables had a statistically significantly increased risk of PD. This study tends to support the hypothesis that environmental factors directly or indirectly related to agricultural activities are associated with the development of PD.

Hochman A, Sternin H, Gorodin S, Korsmeyer S, Ziv I, Melamed E, Offen D. 1998. Enhanced oxidative stress and altered antioxidants in brains of Bcl-2-deficient mice. J Neurochem 71(2):741-748.
Abstract: Bcl-2 is an antiapoptotic protein located in the outer mitochondrial membrane. Cellular perturbations associated with programmed cell death may be the consequence of disrupted mitochondrial function as well as excessive production of reactive oxygen species (ROS). Numerous studies indicate that Bcl-2 is involved in opposing cell death induced by oxidative stimuli, but its mode of action is uncertain. We reexamined the role of Bcl-2 by using a loss-of-function model, Bcl-2 knockout mice. Brains from Bcl-2-deficient mice had a 43% higher content of oxidized proteins and 27% lower number of cells in the cerebellum relative to wild-type mice. Incubation of cerebellar neurons from Bcl-2 +/+ brains with 0.5 nM dopamine caused 25% cell death, whereas in Bcl-2-deficient cells, it resulted in 52% death; glial cells provided protection in both cultures. Splenocytes from Bcl-2-deficient mice were also killed more effectively by dopamine as well as paraquat. Bcl-2-deficient mice did not survive intraperitoneal injection of MPTP, which caused a decrease in

dopamine level in the striatum of Bcl-2 +/- brains, which was more significant than in wild-type mice. When compared with Bcl-2 +/+ brains, brains of 8-day-old Bcl-2-deficient mice had higher activities of the antioxidant enzymes GSH reductase (192%) and GSH transferase (142%), whereas at the age of 30 days, GSH peroxidase was significantly lower (66%). Activities of GSH transferase and GSH reductase increased significantly (158 and 262%, respectively) from day 8 to day 30 in Bcl-2 +/+ mice, whereas GSH peroxidase decreased (31%) significantly in Bcl-2 -/- animals. In summary, our results demonstrated enhanced oxidative stress and susceptibility to oxidants as well as altered levels of antioxidant enzymes in brains of Bcl-2-deficient mice. It is concluded that Bcl-2 affects cellular levels of ROS, which may be due to an effect either on their production or on antioxidant pathways.

Hoglinger GU, Carrard G, Michel PP, Medja F, Lombes A, Ruberg M, Friguet B, Hirsch EC. 2003. Dysfunction of mitochondrial complex I and the proteasome: interactions between two biochemical deficits in a cellular model of Parkinson's disease. J Neurochem 86(5):1297-1307.
Abstract: Two biochemical deficits have been described in the substantia nigra in Parkinson's disease, decreased activity of mitochondrial complex I and reduced proteasomal activity. We analysed interactions between these deficits in primary mesencephalic cultures. Proteasome inhibitors (epoxomicin, MG132) exacerbated the toxicity of complex I inhibitors [rotenone, 1-methyl-4-phenylpyridinium (MPP+ )] and of the toxic dopamine analogue 6-hydroxydopamine, but not of inhibitors of mitochondrial complex II-V or excitotoxins [N -methyl-d-aspartate (NMDA), kainate]. Rotenone and MPP+ increased free radicals and reduced proteasomal activity via adenosine triphosphate (ATP) depletion. 6-hydroxydopamine also increased free radicals, but did not affect ATP levels and increased proteasomal activity, presumably in response to oxidative damage. Proteasome inhibition potentiated the toxicity of rotenone, MPP+ and 6-hydroxydopamine at concentrations at which they increased free radical levels greater than or equal to 40% above baseline, exceeding the cellular capacity to detoxify oxidized proteins reduced by proteasome inhibition, and also exacerbated ATP depletion caused by complex I inhibition. Consistently, both free radical scavenging and stimulation of ATP production by glucose supplementation protected against the synergistic toxicity. In summary, proteasome inhibition increases neuronal vulnerability to normally subtoxic levels of free radicals and amplifies energy depletion following complex I inhibition.

Hoglinger GU, Feger J, Prigent A, Michel PP, Parain K, Champy P, Ruberg M, Oertel WH, Hirsch EC. 2003. Chronic systemic complex I inhibition induces a hypokinetic multisystem degeneration in rats. J Neurochem 84(3): 491-502.
Abstract: In Parkinson's disease, nigral dopaminergic neurones degenerate, whereas post-synaptic striatal target neurones are spared. In some atypical parkinsonian syndromes, both nigral and striatal neurones degenerate. Reduced activity of complex I of the mitochondrial respiratory chain has been implicated in both conditions, but it remains unclear if this

affects the whole organism or only the degenerating brain structures. We therefore investigated the differential vulnerability of various brain structures to generalized complex I inhibition. Male Lewis rats infused with rotenone, a lipophilic complex I inhibitor [2.5 mg/kg/day intraveneously (i.v.) for 28 days], were compared with vehicle-infused controls. They showed reduced locomotor activity and loss of striatal dopaminergic fibres (54%), nigral dopaminergic neurones (28.5%), striatal serotoninergic fibres (34%), striatal DARPP-32-positive projection neurones (26.5%), striatal cholinergic interneurones (22.1%), cholinergic neurones in the pedunculopontine tegmental nucleus (23.7%) and noradrenalinergic neurones in the locus ceruleus (26.4%). Silver impregnation revealed pronounced degeneration in basal ganglia and brain stem nuclei, whereas the hippocampus, cerebellum and cerebral cortex were less affected. These data suggest that a generalized mitochondrial failure may be implicated in atypical parkinsonian syndromes but do not support the hypothesis that a generalized complex I inhibition results in the rather selective nigral lesion observed in Parkinson's disease.

Hoglinger GU, Lannuzel A, Khondiker ME, Michel PP, Duyckaerts C, Feger J, Champy P, Prigent A, Medja F, Lombes A, Oertel WH, Ruberg M, Hirsch EC. 2005. The mitochondrial complex I inhibitor rotenone triggers a cerebral tauopathy. J Neurochem 95(4):930-939.
Abstract: Reduced activity of the mitochondrial respiratory chain - particularly complex I - may be implicated in the etiology of both Parkinson's disease and progressive supranuclear palsy, although these neurodegenerative diseases differ substantially as to their distinctive pattern of neuronal cell loss and the predominance of cerebral alpha-synuclein or tau protein pathology. To determine experimentally whether chronic generalized complex I inhibition has an effect on the distribution of alpha-synuclein or tau, we infused rats systemically with the plant-derived isoflavonoid rotenone. Rotenone-treated rats with a pronounced metabolic impairment had reduced locomotor activity, dystonic limb posture and postural instability. They lost neurons in the substantia nigra and in the striatum. Spherical deposits of alpha-synuclein were observed in a few cells, but cells with abnormal cytoplasmic accumulations of tau immunoreactivity were significantly more numerous in the striatum of severely lesioned rats. Abnormally high levels of tau immunoreactivity were found in the cytoplasm of neurons, oligodendrocytes and astrocytes. Ultrastructurally, tau-immunoreactive material consisted of straight 15-nm filaments decorated by antibodies against phosphorylated tau. Many tau(+) cell bodies also stained positive for thioflavin S, nitrotyrosine and ubiquitin. Some cells with abnormal tau immunoreactivity contained activated caspase 3. Our data suggest that chronic respiratory chain dysfunction might trigger a form of neurodegeneration in which accumulation of hyperphosphorylated tau protein predominates over deposits of alpha-synuclein.

Hoogenraad TU. 1988. Dithiocarbamates and parkinsons-disease. Lancet 1 (8588):767.

Houze P, Chappey O, Gallons H, Scherrmann JM . 1990 Oct. 1-Methyl-4-phenylpyridinium (MPP+) does not exhibit paraquat-like immunoreactivity. Toxicol Lett 53(3):339-42.
Abstract: The structural analogy of paraquat with 1-methyl-4-phenylpyridinium (MPP+) has been implied in the aetiology of Parkinson's disease. The cross-reactivity of MPP+ to a specific antibody to paraquat was assessed by radioimmunoassay and was found to be very low. The results suggest that this polyclonal paraquat antibody does not mimic the MPP+ receptor.

Hsieh BH, Deng JF, Ger J, Tsai WJ. 2001. Acetylcholinesterase inhibition and the extrapyramidal syndrome: A review of the neurotoxicity of organophosphate. Neurotoxicology 22(4):423-427.
Abstract: Organophosphate poisonings are not uncommon, and are the leading cause of death in suicide patients in Taiwan. Acute cholinergic crisis caused by the inhibition of synaptic acetylcholinesterase is the major manifestation of organophosphate poisoning and may cause death within minutes. Delayed neurotoxicities include intermediate syndrome and delayed polyneuropathy have also been described. However, these symptoms may not characterize the complete picture of organophosphate poisoning. Among the 633 patients ever admitted to our hospital with organophosphate poisoning, three patients were found exhibiting impermanent neuromuscular dysfunction, including blepharoclonus, oculogyric crisis, intermittent dystonia, rigidity, and tremor with two of them developing mask face, dyskinesia and akathisia later, following acute cholinergic crisis. The symptoms appeared within 4 days with the duration ranging from 25 days to 2 months. Other causes of the extrapyramidal syndrome noted on these patients ha ve been excluded, and we consider the extrapyramidal syndrome a possible neurotoxic manifestation of organophosphate poisoning, which is transient, needs no treatment, and may be missed because of the critical condition, in a minority of patients. The mechanism remains to be identified, but may be related to the impediment of the function of acetylcholinesterase to modify nigrostriatal dopaminergic system, which is independent of hydrolyzing acetylcholine. More detailed observation for organophosphate poisoned patients and more studies for the biological functions of acetylcholinesterase including the influence on the nigrostriatal dopaminergic system are needed. (C) 2001 Elsevier Science Inc. All rights reserved.

Huang CC. 2004 Mar. Carbon disulfide neurotoxicity: Taiwan experience. Acta Neurol Taiwan 13(1):3-9.
Abstract: Carbon disulfide (CS2) intoxication may induce peripheral neuropathy, encephalopathy, and cardiovascular diseases. In our studies, abnormalities of the peripheral nerves including clinical symptoms and electrophysiological findings were still present 3 years after cessation of CS2 exposure. The data indicate that CS2 neuropathy may persist for a period of time. The involvement of central nervous system may continue even longer. Brain magnetic resonance images usually show multiple high signal intensities in the basal ganglia and subcortical white matter suggesting a vascular event particularly in the small vessels. In addition, a

patient with diffuse demyelination in the cerebral hemispheres also showed a diffuse decrease of regional cerebral blood flow indicating a microangiopathy. Therefore, CS2 exposure should be considered as a risk factor for strokes and one of the causes for diffuse leucoencephalopathy. Because CS2 may induce parkinsonian features, a differential diagnosis between CS2 parkinsonism and idiopathic parkinsonism is important. In our study, dopamine transporter with 99mTc-TRODAT-1 brain single photon emission computed tomography showed a normal uptake in the corpus striatum. The data suggest a normal presynaptic dopaminergic pathway function and provide useful information in differentiation. The involvement of cardiovascular systems may be due to thrombotic effects rather than atherogenic effects. In addition, absorption of CS2 through skin is also significant particularly in workers with skin lesions.

Huang CC, Yen TC, Shih TS, Chang HY, Chu NS. 2004. Dopamine transporter binding study in differentiating carbon disulfide induced parkinsonism from idiopathic parkinsonism. Neurotoxicology 25(3):341-347.
Abstract: Long-term exposure to carbon disulfide (CS2) may induce parkinsonian features. There may be confusion in distinguishing between CS2 parkinsonism and idiopathic parkinsonism, especially for workers who developed parkinsonian features in viscose rayon plants. We performed clinical examinations, and laboratory studies including magnetic resonance imaging (MRI) and dopamine transporter (DAT) studies with Tc-99m-TRODAT-1 brain single photon emission computed tomography (SPECT) in three workers who had long-term exposure to CS2. Patient I had polyneuropathy, and encephalopathy with, tremor; patient 2 had polyneuropathy, and encephalopathy with parkinsonian features; and patient 3 had pure parkinsonian features without polyneuropathy or cerebellar signs. The treatment with L-dopa was effective in patient 3, but non-effective in patient 2. Brain MRI revealed multiple high signal intensities over the subcortical white matter, basal ganglia, and/or even the brainstem inpatients 1 and 2, but normal in patient 3. In DAT studies, the bindings were normal in patients I and 2 and was decreased in patient 3. We conclude that CS2 exposure may induce polyneuropathy, and cerebellar dysfunction in addition to parkinsonian features and that brain MRI may show multiple lesions in the cerebral white matter and basal ganglia. In addition, DAT with Tc-99m-TRODAT-1 brain SPECT may provide a useful information in differential diagnosis between CS2 parkinsonism and idiopathic parkinsonism. (C) 2003 Elsevier Inc. All rights reserved.

Huang J, Liu HQ, Gu WW, Yan Z, Xu ZH, Yang YX, Zhu XZ, Li YP. 2006. A delivery strategy for rotenone microspheres in an animal model of Parkinson's disease. Biomaterials 27(6):937-946.
Abstract: In order to study the pathogenesis of Parkinson's disease (PD), and explore therapeutic drug or approaches, the accurate animal model of PD with inexpensive, biocompatible and convenient administration was necessary. The aim of the present work was to investigate a delivery strategy for rotenone microspheres in an animal model of PD. The rotenone microspheres were prepared by solvent evaporation technique. The rotenone microspheres showed high entrapment efficiency (97.4 +/-

2.2%) with particle size about 100 mu m. In vitro release of rotenone microspheres demonstrated different profiles from medium with different pH or concentration of isopropyl alcohol. The most consistent medium with in vivo rotenone levels in rat plasma was PBS (pH 5.8) with 20% isopropyl alcohol, and the cumulated release amount of rotenone over 30 days was 95.4% in it. The rotenone microspheres (90 mg/kg) produced typical PD symptoms in rats, for example, the cataleptic behavior test demonstrated a obviously prolonged descent latency compared with control animals after administration, and the tyrosine hydroxylase (TH) immunohistochemistry tests showed typical histological evidence of selective degeneration of the nigrostriatal dopaminergic system (striatum and substantia nigra) in rotenone micro spheres-treated rats. In addition, this delivery system for rotenone model showed many noticeable advantages such as inexpensive, biocompatible and expedient administration by direct subcutaneous injection. This information suggested that rotenone microspheres as a delivery strategy for setting up an ideal animal model of PD was feasible. (c) 2005 Elsevier Ltd. All rights reserved.

Hubble JP, Cao T, Hassanein RES, Neuberger JS, Koller WC. 1993. Risk-factors for parkinsons-disease. Neurology 43(9):1693-1697.
Abstract: Parkinson's disease (PD) has been associated with rural living, well-water consumption, and pesticide exposure; however, the individual risk contribution of these variables has not been established. We examined social and medical histories of predominantly rural populations to determine relative risk factors for PD. Patients and controls were surveyed regarding residency, occupation, medical history, and social and dietary habits. An initial multiple logistic regression model was confounded by excessive variable collinearity. Principal factor analysis yielded three factors: rural living (including years of rural residency and ground-water use), pesticide use, and male lifestyle (male gender, head trauma, male-dominated occupations). Other variables did not load in factor analysis and were entered separately, with the three factor scores, in a second multiple logistic regression model. Significant predictors of PD emerged (in order of strength): pesticide use, family history of neurologic disease, and history of depression. The predicted probability of PD was 92.3% (odds ratio = 12.0) with all three predictors positive. Pesticide use (distinguishable from rural living) can be considered a risk factor for the development of PD, with family history of neurologic disease and history of depression serving as weaker predictors of PD.

Hubble JP, Glatt SL, Kurth MC, Schellenberg GD, Hassanein RES, Lieberman AN, Koller WC, Kurth JH. 1995. Cytochrome-p-450 genotype and pesticide exposure as predictors of parkinsons-disease dementia. Am J Hum Genet 57(4):1962.

Hubble JP, Kurth JH, Glatt SL, Kurth MC, Schellenberg GD, Hassanein RES, Lieberman A, Koller WC. 1998. Gene-toxin interaction as a putative risk factor for Parkinson's disease with dementia. Neuroepidemiology 17(2): 96-104.
Abstract: We had previously examined environmental, sociodemographic

and clinical variables as predictors for Parkinson's disease with dementia (PD + D) and found that lower educational attainment, greater motor impairment and advanced age at disease onset were more common in PD + D than in subjects with Parkinson's disease without dementia (PD - D), We now explore the hypothesis that genetic traits coupled with nongenetic factors may raise the risk of development of PD + D, The study cohort of 43 PD + D and 51 PD - D subjects was analyzed examining environmental, sociodemographic and clinical variables along with 3 candidate gene markers: poor debrisoquine metabolizer allele (CYP 2D6 29B+), monoamine oxidase B allele 1, and apolipoprotein E epsilon 4 allele, Variables were initially entered into a multivariate model singly. Again lower education, age at onset and motor impairment appeared as predictors of PD + D while other variables (including allele status) failed to emerge as significant individual risk factors for dementia, We then examined environmental and genetic variables analyzed in tandem to look for potential variable interactions. Subjects who had pesticide exposure and at least I copy of the CYP 2D6 29B+ allele had 83 % predicted probability of PD + D (stepwise logistic regression model: p = 0.0491), This case-control study provides preliminary evidence that a gene-toxin interaction may play an etiological role in PD + D, Further assessment of the role of these putative risk factors in incident dementia in PD is indicated.

Huff RA, Aboudonia MB. 1994. Cis-methyldioxolane specifically recognizes the m2 muscarinic receptor. J Neurochem 62(1):388-391.
Abstract: cis-Methyldioxolane (CD) is a muscarinic receptor agonist. [H-3] CD has been used to label a subpopulation of muscarinic receptors described as exhibiting high agonist affinity. Pharmacological evidence suggests that the population of receptors labeled by [H-3]CD consists of m2 and/or m4 subtypes; however, no studies have directly addressed the subtype selectivity of [H-3]CD. The present study characterizes binding of this ligand to individual human receptor subtypes expressed in transfected Chinese hamster ovary cells. Results indicate that [H-3]CD binds with high affinity only to Hm2 receptors but not to all Hm2 receptors. Twenty-eight percent of Hm2 receptors bound [H-3]CD with a K-D of 3.5 +/- 0.5 nM. Binding was eliminated in the presence of guanosine 5'-O-(3-thiotriphosphate), indicating that the Hm2 receptors labeled by [H-3]CD are those that are associated with GDP-bound G protein. Binding of [H-3]CD by only a subpopulation of Hm2 receptors is in agreement with data generated from studies of [H-3]CD binding in mammalian brain. Because muscarinic receptors have been implicated to play a role in the pathogenesis of both Alzheimer's and Parkinson's disease, as well as the neurotoxicity of organophosphorus compounds, knowledge of the binding specificity of the muscarinic agonist [H-3]CD should aid research in these areas.

Hurwitz A, Hubble JP, Glatt SL, Koller WC, Pollack J. 1995. Erythrocyte thiolmethyltransferase - another failed marker for alzheimers and parkinsons diseases. Neurology 45(10):1903-1906.
Abstract: There are reports that patients with Parkinson's disease (PD) and Alzheimer's disease (AD) have reduced levels of thiolmethyltransferase

(TMT) in erythrocyte membranes. TMT methylates thiols and thiocarbamates, thereby reducing their toxicity. We examined TMT levels in erythrocytes from patients with PD and AD and from age-matched controls. Specific activities of TMT were 564 +/- 199 U/mg protein in PD (n = 32), 513 +/- 118 in AD (n = 13), and 565 +/- 183 in controls (n = 35). There was no difference between any of the groups (p = 0.64). We failed to confirm TMT as a marker for neurodegenerative diseases or for this metabolic defect predisposing to susceptibility to neurotoxins.

Iannone M, Ciriolo MR, Rotilio G, Nistico G. 1991. Intra-nigral infusion of cu-free superoxide-dismutase prevents paraquat-induced behavioral stimulation and ecog epileptogenic discharges in rats. Neuropharmacology 30(8): 893-898.
Abstract: In adult rats, with cannulae chronically implanted by a stereotactic instrument into the substantia nigra (pars compacta), the electrocortical (ECoG) and behavioural effects elicited by intranigral infusion of paraquat and the prevention of these effects by prior administration into the same site of different types of superoxide dismutase, were studied. Paraquat (50-mu-g) produced an intense pattern of behavioural stimulation, contralateral circling and repetitive discharges of high voltage ECoG spikes. The effects of paraquat were abolished in all of the animals pretreated into the same site with copper-free superoxide dismutase. Pretreatment with native Cu, Zn-superoxide dismutase prolonged significantly the latency of onset but did not prevent the behavioural stimulation and ECoG spikes evoked by paraquat. On the contrary, pretreatment with albumin or saline did not confer any protection against the neurotoxicological changes induced by paraquat. In conclusion, the present experiments showed that motor, ECoG and lethal effects of paraquat were completely prevented by Cu-free superoxide dismutase, suggesting that the central effects of this herbicide are in some way related to the release in the brain of copper and/or other transition metal ions.

Ii K. 1995. The role of beta-amyloid in the development of alzheimers-disease. Drugs & Aging 7(2):97-109.
Abstract: Recent molecular biological, biochemical and immunohistochemical studies have revealed various novel facts about beta-amyloidosis including its role in the pathogenesis of Alzheimer's disease (AD). Such discoveries include the finding that beta/A4-amyloid protein (beta-AP) is the major component of the amyloid found in senile plaques (SPs) and amyloid angiopathy, the elucidation of the molecular structures of beta-AP and beta-amyloid protein precursor (APP), the finding that point mutations of APP are involved in some cases of familial AD (FAD), the location of genes for FAD, APP and Down's syndrome on chromosome 21, and of other genes relating to AD on chromosomes 19, 14 and 6, and the successful development of Alzheimer-type neuropathology in transgenic mice overexpressing V717F APP, a mutation of APP. Furthermore, the involvement of various proteases and their inhibitors in metabolism of beta-AP have been suggested by: the presence of Kunitz class serine protease and metalloprotease inhibitor domains on some APP,

the presence of various proteases and inhibitors in SPs and neurofibrillary tangles (NFTs), the involvement of various proteases in the secretory and endosome/lysosome pathways of APP processing, mutation of the APP gene in hereditary cerebral haemorrhage with amyloidosis, Dutch type (HCHWA-D), mutation of the cysteine proteinase inhibitor cystatin C gene in HCHWA-I (Iceland type), and abnormal increases of some proteases or the inhibitors in dystrophic neurites of SP, amyloid of SP, and NFTs. Judging from these reports, dysfunction or deregulation of proteolytic systems may play an important role in beta-amyloid formation. Recent studies of beta-amyloid and various proteases and inhibitors in disorders associated with beta-amyloid formation are reviewed including our 'overload hypothesis' as an underlying event in the dysfunction of proteolytic systems. This information should be helpful to identify targets in the development of drugs for the treatment of AD or other age-related disorders.

Inden M, Kitamura Y, Sanada H, Tsuchishita Y, Taniguchi T, Watanabe K. 2002. Rotenone-treated planarian: A unique parkinsonian model of invertebrate flatworm. Jpn J Pharmacol 88:180P.

Inden M, Kondo J, Kitamura Y, Takata K, Tsuchiya D, Nishimura K, Taniguchi T, Sawada H, Shimohama S. 2003. Differences in rotational asymmetry in rats caused by single intranigral injections of 6-hydroxydopamine, 1-methyl-4-phenylpyridinium ion and rotenone. Biogenic Amines 17(4-6): 281-291.
Abstract: Recently, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenylpyridinium ion (MPP+) and rotenone have been shown to be dopaminergic neurotoxins. However, their neurotoxicities in rat brains in vivo are not fully understood. In the present study, we compared the in vivo neurotoxicities of 6-OHDA, MPP+ and rotenone using a single intranigral injection. The injection of 6-OHDA caused the greatest loss of dopaminergic neurons in both the substantia nigra and striatum, and apomorphine induced contralateral rotation. In contrast, apomorphine-induced rotational behavior was in the ipsilateral direction with MPP+, and was not observed with rotenone. Although MPPI and rotenone caused a loss of dopaminergic neurons in the substantia nigra, striatal neurodegeneration varied. These results suggest that intranigral injections of these neurotoxins produce different degrees of doparninergic neurotoxicity in rats in vivo.

Ito Y, Ushitora H. 2006. Trapping of carbamic acid species with (trimethylsilyl) diazomethane. Tetrahedron 62(1):226-235.
Abstract: Methoxycarbonylation of a variety of amines into the corresponding methyl carbamates was accomplished by allowing them to react with (trimethylsilyl)diazomethane TMSCHN2 under bubbling of CO2. The reaction was performed at room temperature for a period of ca. 2h in benzene-MeOH (4/1 v/v), which was the solvent of choice. In this mixed solvent, undesirable bicarbonate is formed in equilibrium along with carbamate anion. Owing to the irreversibility in the esterification step by TMSCHN2, however, the yield of methyl carbamate can reach very high.

Jacobsson SOP, Fowler CJ. 1999. Dopamine and glutamate neurotoxicity in cultured chick telencephali cells: effects of NMDA antagonists, antioxidants and MAO inhibitors. Neurochem Int 34(1):49-62.
Abstract: In a recent study, it was found that the intrastriatal administration to rats of the organophosphorous compound soman and kainic acid produced a rapid release not only of glutamate but also of dopamine in this brain region. Dopamine is a potent source of free radicals and is known to produce cytotoxic effects, per se. This raises the possibility that the released glutamate and dopamine act synergistically to produce the neurotoxicity found after soman administration. In order to investigate the feasibility of this hypothesis in an in vitro system. the effects of dopamine and glutamate upon cell survival were investigated using chick neurons (7 DIV) in serum-free primary culture. The neurons were treated with dopamine and/or glutamate for up to 24 h and cell toxicity was then assessed either by determination of cell densities, by the release of cytoplasmic LDH or by the MTT cytotoxicity assay. L-Glutamate produced a concentration-dependent cytotoxicity that was seen as early as after 30 min of exposure, and was accompanied by an increased level of lipid peroxidation. The L-glutamate toxicity could to a large extent be prevented by NMDA receptor antagonists and to a lesser extent by catalase, superoxide dismutase or glutathione ethyl ester added 30 min before the glutamate. Dopamine was also cytotoxic, and the cytotoxicity was reduced by the combination of catalase and glutathione ethyl ester but not by the MAO inhibitors clorgyline or L-deprenyl, or by the selective dopamine uptake inhibitor GBR 12783. The cytotoxic effects of dopamine and L-glutamate were additive rather than synergistic, regardless of the incubation time used. It is concluded that chick neurons in serum-free culture are a useful in vitro model system for the study of cell toxicity produced by oxidative stress and by glutamate. The cytotoxic effects of dopamine in this model are not due to the monoamine oxidase-mediated production of hydrogen peroxide but appear at least in part to be related to oxidative stress. (C) 1999 Elsevier Science Ltd. All rights reserved.

Janaky R, Varga V, Hermann A, Saransaari P, Oja SS. 2000. Mechanisms of L-cysteine neurotoxicity. Neurochem Res 25(9-10):1397-1405.
Abstract: We review here the possible mechanisms of neuronal degeneration caused by L-cysteine, an odd excitotoxin. L-Cysteine lacks the omega carboxyl group required for excitotoxic actions via excitatory amino acid receptors, yet it evokes N-methyl-D-aspartate (NMDA) -like excitotoxic neuronal death and potentiates the Ca2+ influx evoked by NMDA. Both actions are prevented by NMDA antagonists. One target for cysteine effects is thus the NMDA receptor. The following mechanisms are discussed now: (1) possible increase in extracellular glutamate via release or inhibition of uptake/degradation, (2) generation of cysteine alpha -carbamate, a toxic analog of hTMDA, (3) generation of toxic oxidized cysteine derivatives, (4) chelation of Zn2+ which blocks the NMDA receptor-ionophore, (5) direct interaction with the NMDA receptor redox site(s), (6) generation of free radicals, and (7) formation of S-

nitrosocysteine. In addition to these, we describe another new alternative for cytotoxicity: (8) generation of the neurotoxic catecholamine derivative, 5-S-cysteinyl-3,4-dihydroxyphenylacetate (cysdopac).

Jenner P. 2001. Parkinson's disease, pesticides and mitochondrial dysfunction. Trends Neurosci 24(5):245-246.

Jensen PJ, Alter BJ, O'malley KL. 2003. alpha-synuclein protects naive but not dbcAMP-treated dopaminergic cell types from 1-methyl-4-phenylpyridinium toxicity. J Neurochem 86(1):196-209.
Abstract: The pre-synaptic protein, alpha-synuclein, has been associated with the pathogenesis of Parkinson's disease. The present study indicates that alpha-synuclein, but not its mutants (A53T, A30P), can protect CNS dopaminergic cells from the parkinsonism-inducing drug 1-methyl-4-phenylpyridinium (MPP+ ), whereas it cannot protect from the dopaminergic toxin, 6-hydroxydopamine, hydrogen-peroxide, or the beta-amyloid peptide, A-beta. Protection from MPP+ was directly correlated with the preservation of mitochondrial function. Specifically, alpha-synuclein rescued cells from MPP+ mediated decreases in mitochondrial dehydrogenase activity and loss of ATP levels by utilizing ketosis. It also prevented toxin-induced activation of the creatine kinase/creatine phosphate system. Similarly, alpha-synuclein protected cells from the complex I inhibitor rotenone and 3-nitroproprionic acid, a complex II inhibitor. Wild-type alpha-synuclein-mediated neuroprotection and subsequent alterations in energy were not found in dbcAMP-differentiated cells. These results suggest that the normal physiological role for alpha-synuclein may change during development.

Jiang HB, Ren Y, Zhao JH, Feng J. 2004. Parkin protects human dopaminergic neuroblastoma cells against dopamine-induced apoptosis. Hum Mol Genet 13(16): 1745-1754.
Abstract: Parkinson's disease (PD) is characterized by the selective degeneration of dopaminergic (DA) neurons in substantia nigra pars compacta (SNpc). A combination of genetic and environmental factors contributes to such a specific loss. Among the five PD-linked genes identified so far, parkin, a protein-ubiquitin E3 ligase, appears to be the most prevalent genetic factor in PD. Although a variety of substrates have been identified for parkin, none of them is selectively expressed in nigral DA neurons. It remains unclear how accumulation of these substrates in the absence of functional parkin may cause the selective death of DA neurons in SNpc. Here, we show that overexpression of parkin protected human DA neuroblastoma cell line (SH-SY5Y) against apoptosis induced by DA or 6-OHDA, but not by H2O2 or rotenone. Parkin significantly attenuated dopamine-induced activation of c-Jun N-terminal kinase (JNK) and caspase-3. It also decreased the level of reactive oxygen species (ROS) and protein carbonyls in the cell. Inhibiting DA uptake through dopamine transporter or treating the cell with antioxidants significantly reduced oxidative stress and dopamine toxicity. Furthermore, PD-linked mutations of parkin significantly abrogated the protective effect of wild-type parkin, as well as its ability to suppress ROS and protein

carbonylation. These results suggest that parkin protects against dopamine toxicity by decreasing oxidative stress and ensuing activation of apoptotic programs such as the JNK/caspase pathway. This protective function of parkin, which is greatly attenuated by its PD-linked mutations, may be uniquely important for the survival of DA neurons, as they are constantly threatened by oxyradicals produced during dopamine oxidation.

Jimenezjimenez FJ, Mateo D, Gimenezroldan S. 1992. Exposure to well water and pesticides in parkinsons-disease - a case-control study in the madrid area. Mov Disord 7(2):149-152.
Abstract: Past exposure to well water and pesticides was assessed in 128 unselected Parkinson's disease (PD) patients and 256 age and sex-matched controls. All were residents in a defined urban area of Madrid, Spain. In keeping with other reports, we found that exposure to well water might be a factor associated with the likelihood of developing PD, though only prolonged exposures of 30 years or longer were significantly different between PD and controls ($p < 0.02$). In contrast, past exposure to pesticides did not appear to be associated with an increased risk of developing PD. Prolonged well water drinking antedating the development of PD was not associated with early onset of the disease, nor did such cases progress to greater disability. Future case-control studies addressing prolonged well water consumption as a risk factor in PD should look for differences in the content of substances other than pesticides in the water as determined by the source of water to which patients may have been specifically exposed.

Johannessen JN, Adams JD, Schuller HM, Bacon JP, Markey SP. 1986 Feb 24. 1-Methyl-4-phenylpyridine (MPP+) induces oxidative stress in the rodent. Life Sci 38(8):743-9.
Abstract: MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) produces an irreversible parkinsonism in primates. Recent evidence suggests metabolism of MPTP to 1-methyl-4-phenylpyridine (MPP+) is required for toxicity. We have proposed that MPP+ may play a central role in the toxicity of MPTP, but direct assessment of the effects of MPP+ in brain is difficult. Therefore, we have sought to define the mechanism of peripheral MPP+ toxicity in the rat and mouse. Systemically administered MPP+ produced its major pathology in the lung and was typified by perivascular edema. An increase in plasma glutathione disulfide concentrations also resulted, suggesting that MPP+ in analogy to paraquat produces oxidative stress. In addition, the lethality of MPP+ in the mouse was increased by dietary selenium deficiency. These results define in both pathological and chemical terms the potent systemic toxicity of MPP+ and suggest that MPP +, because of its high concentration in primate brain, has the potential to play an important role in the CNS toxicity of MPTP.

Joost O, Taylor CA, Thomas CA, Cupples LA, Saint-Hilaire MH, Feldman RG, Baldwin CT, Myers RH. 1999. Absence of effect of seven functional mutations in the CYP2D6 gene in Parkinson's disease. Mov Disord 14(4): 590-595.
Abstract: The reduction or loss of cytochrome P450 enzyme activity as a

result of mutations in the CYP2D6 gene has been suggested as a risk factor for Parkinson's disease (PD). Conflicting, results among reported studies of the prevalence of mutations among patients with PD suggested a more comprehensive genotyping and an analysis of the interactions with other suspected risk factors and family history. We determined the frequency of seven CYP2D6 mutations among 109 patients with PD and 110 control subjects. Family history of PD, age of onset, exposure to pesticides or herbicides, and well-water consumption were obtained for all cases. There was no significant difference in frequency between patients with PD and control subjects for any mutant allele and no significant association with family history, onset age, or environmental exposures. We sought to increase the power of our study by combining reports from the literature, choosing allele frequencies as the most informative measure. Although we found variability in reported allele frequencies for control subjects that made a metaanalysis problematic, summing all reports demonstrated no difference in CYP2D6 mutation frequency between patients with PD and control subjects. This comprehensive study of CYP2D6 mutations demonstrates that other genes or shared environmental exposures account for the familial risk of PD.

Jorgenson JL. 2001. Aldrin and Dieldrin: A review of research on their production, environmental deposition and fate, bioaccumulation, toxicology and epidemiology in the United States. Environ Health Perspect 109:113-139.
Abstract: In the last decade four international agreements have focused on a group of chemical substances known as persistent organic pollutants (POPs). Global agreement on the reduction and eventual elimination of these substances by banning their production and trade is a long-term goal. Negotiations for these agreements have focused on the need to correlate data from scientists working on soil and water sampling and air pollution monitoring. Toxicologists and epidemiologists have focused on wildlife and human health effects and understanding patterns of disease requires better access to these data. in the last 20 years, substantial databases have been created and now are becoming available on the Internet. This review is a detailed examination of 2 of the 12 POPs, aldrin and dieldrin, and how scientific groups identify and measure their effects. It draws on research findings from a variety of environmental monitoring networks in the United States. An overview of the ecologic and health effects of aldrin and dieldrin provides examples of how to streamline some of the programs and improve access to mutually useful scientific data. The research groups are located in many government departments, universities, and private organizations. Identifying databases can provide an "information accelerator" useful to a larger audience and can help build better plant and animal research models across scientific fields.

Kabuto H, Nishizawa M, Tada M, Higashio C, Shishibori T, Kohno M. 2005. Zingerone [4-(4-hydroxy-3-methoxyphenyl)-2-butanone] prevents 6-hydroxydopamine-induced dopamine depression in mouse striatum and increases superoxide scavenging activity in serum. Neurochem Res 30(3): 325-332.
Abstract: As superoxide (O-2(-)) and hydroxyl radical (OH) have been

implicated in pathogenesis of Parkinson's disease, free radical scavenging, antioxidant, and neuroprotective agents have attracted attention as ways to prevent progression. We examined effects of zingerone, an alkaloid extracted from ginger root, on 6-hydroxydopamine (6-OHDA)-induced dopamine (DA) reduction in mouse striatum. Zingerone administration 1 h before and for 6 more days following one intracerebroventricular 6-OHDA injection prevented reductions of striatal DA and its metabolites, and increased serum O-2(-) scavenging activity. Zingerone did not change activities of catalase or glutathione peroxidase in striatum or serum, or O-2 (-) scavenging activity in striatum. Treatment with diethyldithiocarbamate, SOD inhibitor, abolished the protective effect of zingerone against 6-OHDA-induced DA reduction. In vitro, zingerone scavenged O-2(-) and OH and suppressed lipid peroxidation only weakly. Thus, direct antioxidant effects may be a minor component of its putative neuroprotective effect; instead, zingerone acted mainly by increasing systemic superoxide dismutase activity. Effects of zingerone treatment in this model suggest possible value in treatment of Parkinson's disease.

Kahle PJ, Haass C. 2001 Feb. The emerging utility of animal models of chronic neurodegenerative diseases. Expert Opin Ther Targets 5 (1):125-32. Abstract: The two most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). The symptoms are caused by the initially selective degeneration of neuronal subpopulations involved in memory (AD) or movement control (PD). The cause of both diseases is unknown, but ageing is an inevitable risk factor. The identification of disease-associated genes was a breakthrough for the understanding of molecular mechanisms of neurodegeneration and has provided the basis for the establishment of cell culture and animal model systems, instrumental for target validation and drug screening. Familial AD is caused by mutations in the beta-amyloid precursor protein (betaAPP) and in the gene products responsible for its proteolytic processing, namely the presenilins. Transgenic mice expressing these mutant genes develop characteristic AD plaques in an age-dependent manner. A reduction of plaque burden and amelioration of cognitive decline in these animals was recently achieved by vaccination with amyloid beta-protein fibrils. The other hallmark lesion of AD, the neurofibrillary tangle, has been modelled recently in transgenic mice expressing mutant tau protein linked to frontotemporal dementia. PD is characterised by intraneuronal cytoplasmic deposits (Lewy bodies) of the PD-associated gene product alpha-synuclein. Transgenic expression of alpha-synuclein recreated hallmark features of PD in mice and fruit flies, establishing alpha-synuclein as PD-causing drug target. Moreover, environmental risk factors such as the pesticide rotenone have been used successfully to generate rodent models of PD. Lesion models of PD are being exploited for the development of experimental gene therapy and transplantation approaches.

Kamel F, Hoppin JA. 2004. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect 112(9):950-958. Abstract: Poisoning by acute high-level exposure to certain pesticides has well-known neurotoxic effects, but whether chronic exposure to moderate

levels of pesticides is also neurotoxic is more controversial. Most studies of moderate pesticide exposure have found increased prevalence of neurologic symptoms and changes in neurobehavioral performance, reflecting cognitive and psychomotor dysfunction. There is less evidence that moderate exposure is related to deficits in sensory or motor function or peripheral nerve conduction, but fewer studies have considered these outcomes. It is possible that the most sensitive manifestation of pesticide neurotoxicity is a general malaise lacking in specificity and related to mild cognitive dysfunction, similar to that described for Gulf War syndrome. Most studies have focused on organophosphate insecticides, but some found neurotoxic effects from other pesticides, including fungicides, fumigants, and organochlorine and carbamate insecticides. Pesticide exposure may also be associated with increased risk of Parkinson disease; several classes of pesticides, including insecticides, herbicides, and fungicides, have been implicated. Studies of other neurodegenerative diseases are limited and inconclusive. Future studies will need to improve assessment of pesticide exposure in individuals and consider the role of genetic susceptibility. More studies of pesticides other than organophosphates are needed. Major unresolved issues include the relative importance of acute and chronic exposure, the effect of moderate exposure in the absence of poisoning, and the relationship of pesticide-related neurotoxicity to neurodegenerative disease.

Kamel F, Tanner C, Hoppin J, Umbach D, Chan P, Langston J, Blair A, Sandler D. 2000. Pesticides and Parkinson's disease: The agricultural health study. Epidemiology 11(4):S149.

Kamijo Y, Soma K, Fukuda M, Asari Y, Ohwada T. 1999. Rabbit syndrome following phenol ingestion. J Toxicol Clin Toxicol 37(4):509-11.
Abstract: CASE REPORT: An elderly Japanese woman ingested a massive quantity of phenol in a suicide attempt. She was admitted to the Emergency Department in respiratory arrest and deep coma. Duodenogastritis was evident endoscopically. With the return of spontaneous respiration and consciousness, fine, rapid rhythmic perioral movements developed together with Parkinsonian findings. The abnormal movements were aggravated by administration of a neuroleptic and ameliorated by discontinuing the drug; they disappeared completely by hospital day 15. In addition to neuroleptic drugs, phenol intoxication may cause the rabbit syndrome by inducing cholinergic dominance with relative dopamine hypofunction in the central nervous system.

Kane FJ Jr. 1970 Nov. Carbon disulfide intoxication from overdosage of disulfiram. Am J Psychiatry 127(5):690-4.

Kanthasamy A. 2003. A novel proteolytic activation of PKC delta promotes apoptotic cell death in dopaminergic neuronal cells during pesticide exposures: Relevance to environmental factors and Parkinson's disease. Neurotoxicology 24(2):291-292.

Kanthasamy A, Anantharam V, Kanthasamy A. 2004. Role of oxidative stress-

sensitive kinase in dieldrin-induced dopaminergic cell death: Relevance to Parkinson's disease. Neurotoxicology 25(4):702-703.

Kanthasamy AG, Kitazaw M, Kaul S, Yang Y, Lahiri DK, Anantharam V, Kanthasamy A. 2003. Proteolytic Activation of Proapoptotic Kinase Pkc Delta Is Regulated by Overexpression of Bcl-2 Implications for Oxidative Stress and Environmental Factors in Parkinson's DiseaseVolume 1010. p 683-686. Apoptosis: From Signaling Pathways to Therapeutic Tools: Annals of the New York Academy of Sciences.
Abstract: We previously demonstrated that the organochlorine pesticide dieldrin, a potential chemical risk factor for development of Parkinson's disease (PD), impairs mitochondrial function and promotes apoptosis in dopaminergic PC12 cells. We further demonstrated that caspase-3-dependent proteolytic activation of a member of the novel PKC family, protein kinase Cdelta (PKCdelta), contributes to apoptotic cell death in dopaminergic cells. In the present study, we report that the proapoptotic function of PKCdelta can be regulated by overexpression of the mitochondrial anti-apoptotic protein Bcl2 in dieldrin-treated dopaminergic cells. Exposure to dieldrin (30 or 100 muM) for 3 h produced a dose-dependent increase in caspase-3 activation and DNA fragmentation in vector-transfected PC12 cells. Overexpression of human Bcl-2 in PC12 cells completely suppressed dieldrin-induced caspase-3 activation and DNA fragmentation. Furthermore, dieldrin-induced proteolytic activation of PKCdelta was also remarkably reduced in Bcl-2-overexpressed cells. Together, these results suggest that the proapoptotic function of PKCdelta can be regulated by mitochondrial redox modulators during neurodegenerative processes.

Kanthasamy AG, Kitazawa M, Kanthasamy A, Anantharam V. 2005. Dieldrin-induced neurotoxicity: Relevance to Parkinson's disease pathogenesis. Neurotoxicology 26(4):701-719.
Abstract: Parkinson's disease (PD) is increasingly recognized as a neurodegenerative disorder strongly associated with environmental chemical exposures. Recent epidemiological data demonstrate that environmental risk factors may play a dominant role as compared to genetic factors in the etiopathogenesis of idiopathic Parkinson's disease. Identification of key genetic defects such as alpha-synuclein and parkin mutations in PD also underscores the important role of genetic factors in the disease. Thus, understanding the interplay between genes and environment in PD may be critical to unlocking the mysteries of this 200-year-old neurodegenerative disease. Pesticides and metals are the most common classes of environmental chemicals that promote dopaminergic degeneration. The organochlorine pesticide dieldrin has been found in human PD postmortem brain tissues, suggesting that this pesticide has potential to promote nigral cell death. Though dieldrin has been banned, humans continue to be exposed to the pesticide through contaminated dairy products and meats due to the persistent accumulation of the pesticide in the environment. This review summarizes various neurotoxic studies conducted in both cell culture and animals models following dieldrin exposure and discusses their relevance to key pathological mechanisms

associated with nigral dopaminergic degeneration including oxidative stress, mitochondrial dysfunction, protein aggregation, and apoptosis. (c) 2004 Elsevier Inc. All rights reserved.

Kanthasamy AG, Kitazawa M, Kaul S, Yang Y, Lahiri DK, Anantharam V, Kanthasamy A. 2003 Dec. Proteolytic activation of proapoptotic kinase PKCdelta is regulated by overexpression of Bcl-2: implications for oxidative stress and environmental factors in Parkinson's disease. Ann N Y Acad Sci 1010:683-6.
Abstract: We previously demonstrated that the organochlorine pesticide dieldrin, a potential chemical risk factor for development of Parkinson's disease (PD), impairs mitochondrial function and promotes apoptosis in dopaminergic PC12 cells. We further demonstrated that caspase-3-dependent proteolytic activation of a member of the novel PKC family, protein kinase Cdelta (PKCdelta), contributes to apoptotic cell death in dopaminergic cells. In the present study, we report that the proapoptotic function of PKCdelta can be regulated by overexpression of the mitochondrial anti-apoptotic protein Bcl2 in dieldrin-treated dopaminergic cells. Exposure to dieldrin (30 or 100 micro M) for 3 h produced a dose-dependent increase in caspase-3 activation and DNA fragmentation in vector-transfected PC12 cells. Overexpression of human Bcl-2 in PC12 cells completely suppressed dieldrin-induced caspase-3 activation and DNA fragmentation. Furthermore, dieldrin-induced proteolytic activation of PKCdelta was also remarkably reduced in Bcl-2-overexpressed cells. Together, these results suggest that the proapoptotic function of PKCdelta can be regulated by mitochondrial redox modulators during neurodegenerative processes.

Karen DJ, Li W, Harp PR, Gillette JS, Bloomquist JR. 2001. Striatal dopaminergic pathways as a target for the insecticides permethrin and chlorpyrifos. Neurotoxicology 22(6):811-817.
Abstract: Because insecticide exposure has been linked to both Parkinsons disease and Gulf War illness, the neurotoxic actions of pyrethroid and organophosphate insecticides on behavior and striatal dopaminergic pathways were investigated in C57BL/6 mice treated with permethrin (three i.p. doses at 0.2-200 mg/kg) or chlorpyrifos (three s.c. doses at 25-100 mg/kg) over a 2-week period. Permethrin altered maximal [H-3] dopamine uptake in striatal synaptosomes from treated mice, with changes in V-max displaying a bell-shaped curve. Uptake was increased to 134% of control at a dose of 1.5 mg/kg. At higher doses of PM (25 mg/kg), dopamine uptake declined to a level significantly below that of control (50% of control at 200 mg/kg, $P<0.01$). We also observed a small, but statistically significant decrease in [H-3]dopamine uptake by chlorpyrifos, when given at a dose of 100 mg/kg. There it-as no significant effect on the K-m for dopamine transport. Evidence of cell stress was observed in measures of mitochondrial function, which were reduced in mice given high-end doses of chlorpyrifos and permethrin. Although cytotoxicity was not reflected in decreased levels of striatal dopamine in either 200 mg/kg PM or 100 mg/kg CPF treatment groups, an increase in dopamine turnover at 100 mg/kg CPF was indicated by a significant increase in titers of the

dopamine metabolite, 3,4-dihydroxyphenylacetic acid. Both permethrin and chlorpyrifos caused a decrease in open field behavior tit the highest closes tested. Although frank Parkinsonism was not observed, these findings confirm that dopaminergic neurotransmission is affected by exposure to pyrethroid and organophosphorus insecticides, and may contribute to the overall spectrum of neurotoxicity caused by, these compounds. (C) 2001 Elsevier Science Inc. All rights reserved.

Kaur N, Lu B, Monroe RK, Ward SM, Halvorsen SW. 2005. Inducers of oxidative stress block ciliary neurotrophic factor activation of Jak/STAT signaling in neurons. J Neurochem 92(6):1521-1530.
Abstract: Generation of reactive oxygen species (ROS) with the accumulation of oxidative damage has been implicated in neurodegenerative disease and in the degradation of nervous system function with age. Here we report that ROS inhibit the activity of ciliary neurotrophic factor (CNTF) in nerve cells. Treatment with hydrogen peroxide (H2O2) as a generator of ROS inhibited CNTF-mediated Jak/STAT signaling in all cultured nerve cells tested, including chick ciliary ganglion neurons, chick neural retina, HMN-1 motor neuron hybrid cells, and SH-SY5Y and BE(2)-C human neuroblastoma cells. H2O2 treatment of non-neuronal cells, chick skeletal muscle and HepG2 hepatoma cells, did not inhibit Jak/STAT signaling. The H2O2 block of CNTF activity was seen at concentrations as low as 0.1 mM and within 15 min, and was reversible upon removal of H2O2 from the medium. Also, two other mediators of oxidative stress, nitric oxide and rotenone, inhibited CNTF signaling. Treatment of neurons with H2O2 and rotenone also inhibited interferon-gamma-mediated activation of Jak/STAT1. Depleting the intracellular stores of reduced glutathione by treatment of BE(2)-C cells with nitrofurantoin inhibited CNTF activity, whereas addition of reduced glutathione protected cells from the effects of H2O2. These results suggest that disruption of neurotrophic factor signaling by mediators of oxidative stress may contribute to the neuronal damage observed in neurodegenerative diseases and significantly affect the utility of CNTF-like factors as therapeutic agents in preventing nerve cell death.

Kim DK, Kim JS, Kim JE, Kim SJ, Lee JS, Kim DJ, Son JH, Chun HS. 2005. Heme oxygenase-I induction by dieldrin in dopaminergic cells. Neuroreport 16(5): 509-512.
Abstract: We investigated the transcriptional events and signaling pathways involved in the induction of heme oxygenase-1 (HO-1) by dieldrin, an environmental risk factor of Parkinson's disease, in a dopaminergic neuronal cells (SN4741). Dieldrin exposure caused dose-dependent and time-dependent induction of heme oxygenase activity and HO-I protein expression. Deletional and mutational analyses showed that the 5' distal enhancers, E1 and E2, mediate dieldrin- induced HO-1 gene transcription, and the AP-1 DNA binding sites in the E2 enhancer are critical for E2-mediated HO-1 gene activation. Furthermore, both the p38 and JNK mitogen-activated protein kinase pathways are utilized for HO-1 transcriptional activation by dieldrin. HO-1 inhibitor, ZnPP IX reduced the expression of HO-1 but enhanced the cytotoxicity induced by dieldrin. (c)

2005 Lippincott Williams W Wilkins.

Kim KS, Choi SY, Kwon HY, Woo MH, Kang TC, Kang JH. 2002. Aggregation of alpha-synuclein induced by the Cu,Zn-superoxide dismutase and hydrogen peroxide system. Free Radic Biol Med 32(6):544-550.
Abstract: Alpha-synuclein is a major component of the abnormal protein aggregation in Lewy bodies of Parkinson's disease (PD) and senile plaques of Alzheimer's disease (AD). Previous studies have shown that the aggregation of alpha-synuclein was induced by copper (11) and H2O2 system. Since copper ions could be released from oxidatively damaged Cu,Zn-superoxide dismutase (SOD), we investigated the role of Cu,Zn-SOD in the aggregation of alpha-synuclein. When alpha-synuclein was incubated with both Cu,Zn-SOD and H2O2, alpha-synuclein was induced to be aggregated. This process was inhibited by radical scavengers and spin trapping agents such as 5,5'-dimethyl 1-pyrolline N-oxide and tert-butyl-alpha-phenylnitrone. Copper chelators, diethyldithiocarbamate and penicillamine, also inhibited the Cu,Zn-SOD/H2O2 system-induced alpha-synuclein aggregation. These results suggest that the aggregation of alpha-synuclein is mediated by the Cu,Zn-SOD/H2O2 system via the generation of hydroxyl radical by the free radical-generating function of the enzyme. The Cu,Zn-SOD/H2O2-induced alpha-synuclein aggregates displayed strong thioflavin-S reactivity, reminiscent of amyloid. These results suggest that the Cu,Zn-SOD/H2O2 system might be related to abnormal aggregation of alpha-synuclein, which may be involved in the pathogenesis of PD and related disorders. (C) 2002 Elsevier Science Inc.

Kim SJ, Kim JE, Moon IS. 2004. Paraquat induces apoptosis of cultured rat cortical cells. Mol Cells 17(1):102-107.
Abstract: Paraquat (PQ; 1,1'-dimethyl-4,4'-bipyridinium dichloride) is widely used as a universal herbicide. Although systemic treatment with PQ gives rise to the highest level of the herbicide in the cerebral cortex, our knowledge of its effects in this brain region is very limited. We took advantage of rat cortical cell cultures to analyze how PQ affects cortical neurons. Lactate dehydrogenase (LDH) assay and propidium iodide (PI) staining showed that PQ was cytotoxic to cortical neurons with an IC50 on the third day after treatment of similar to10 muM. PQ-treated cells had shrunken soma with condensed nuclei and disintegrated dendrites, typical signs of apoptosis. Immunocytochemistry of 8-day in vitro (DIV) cells one day after PQ treatment with antiphospho-H2AX antibody showed that the average number of punctae per nucleus had increased several-fold, indicating substantial DNA fragmentation. Furthermore, double-staining of 7.5 DIV cultures (50 muM PQ) with PI and an antibody against annexin V (AN), an impermeable plasma protein which specifically binds to phosphatidylserine (PS), showed that the percentages of AN(+)/PI(-) cells had also increased several-fold, pointing to considerable movement of PS from the inner to the outer leaflet of the plasma membrane. Taken together, our data indicate that PQ induces apoptosis in cortical cell cultures.

Kimura M, Masuda T, Yamada K, Mitani M, Kubota N, Kawakatsu N, Kishii K, Inazu

M, Kiuchi Y, Oguchi K, Namiki T. 2003. Syntheses of novel diphenyl piperazine derivatives and their activities as inhibitors of dopamine uptake in the central nervous system. Bioorganic & Medicinal Chemistry 11(8): 1621-1630.
Abstract: A new series of diphenyl piperazine derivatives containing the phenyl substituted aminopropanol moiety, which were modified at sites between the diphenyl and piperazine moieties, was prepared and evaluated for dopamine transporter binding affinity with [H-3]GBR12935 in rat striatal membranes. These synthesized compounds showed apparent dopamine transporter binding affinities (IC50 <30 nM) and some of them were approximately equivalent in activity to GBR12909 known as a potent dopamine uptake inhibitor, showing the activities with IC50 values of nanomolar range. Among them, 1-[4,4-bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(phenylamino)propyl]pipe razine 2 was evaluated for extracellular dopamine levels in rat striatum using in vivo brain microdialysis. The intraperitoneal administration of 2 (0.01, 0.03, or 0.1 mmol/kg) induced dose-dependent increases of dopamine levels in rat striatal dialysates. The maximum increases in dopamine levels induced by 2 were greater than those by GBR12909. The pharmacological data of these novel diphenyl piperazine derivatives show that the compounds have potent dopamine uptake inhibitory activities in the central nervous system. (C) 2003 Elsevier Science Ltd. All rights reserved.

King TD, Bijur GN, Jope RS. 2001. Caspase-3 activation induced by inhibition of mitochondrial complex I is facilitated by glycogen synthase kinase-3 beta and attenuated by lithium. Brain Res 919(1):106-114.
Abstract: The compound 1-methyl-4-phenylpyridinium (MPP) is, a selective inhibitor of mitochondrial complex L and is widely used in model systems to elicit neurochemical alterations that may be associated with Parkinson's disease. In the present study treatment of human neuroblastoma, SH-SY5Y cells with MPP resulted in a time- and concentration-dependent activation of the apoptosis-associated cysteine protease caspase-3, and caused morphological changes characteristic of apoptosis. To test if the activation state of the cell survival-promoting phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway affects MPP-induced caspase-3 activation, PI3K was inhibited with LY294002, or activated with insulin-like growth factor-1. MPP-induced caspase-3 activation was increased by inhibition of PI3K, and decreased by stimulation of PI3K, indicative of anti-apoptotic signaling by the PI3K/Akt pathway. To test if glycogen synthase kinase-3 beta (GSK3 beta), a pro-apoptotic kinase that is inhibited by Akt, is involved in regulating MPP-induced apoptosis, overexpression of GSK3 beta and lithium, a selective inhibitor of GSK3 beta, were used to directly alter GSK3 beta activity. MPP-induced caspase-3 activity was increased by overexpression of GSK3 beta. Conversely, the GSK3 beta inhibitor lithium attenuated MPP-induced caspase-3 activation. To test if these regulatory interactions applied to other mitochondrial complex I inhibitors, cells were treated with rotenone. Rotenone-induced activation of caspase-3 was enhanced by inhibition of PI3K or increased GSK3 beta activity, and was attenuated by inhibiting GSK3 beta with lithium. Overall, these results

indicate that inhibition of GSK3 beta provides protection against the toxic effects of agents, such as MPP and rotenone, that impair mitochondrial function. (C) 2001 Published by Elsevier Science B.V.

King TD, Jope RS. 2005. Inhibition of glycogen synthase kinase-3 protects cells from intrinsic but not extrinsic oxidative stress. Neuroreport 16(6): 597-601.
Abstract: Oxidative stress is linked to neuronal dysfunction and death in many diseases. Glycogen synthase kinase-3 often promotes apoptosis, so this investigation tested whether glycogen synthase kinase-3 is linked to oxidative stress-induced apoptosis. Both intrinsic oxidative stress induced by the mitochondrial inhibitor rotenone and extrinsic oxidative stress induced by exogenously added H2O2 activated Bax, caspase-2, and caspase-3 in human neuroblastoma SH-SY5Y cells. Inhibitors of glycogen synthase kinase-3 blocked rotenone-induced, but not H2O2-induced, activation of both caspases, but not Bax activation. Thus, glycogen synthase kinase-3 is an important component of intrinsic oxidative stress-induced apoptosis that acts downstream of mitochondrial Bax activation, and there are substantial differences in the role of glycogen synthase kinase-3, and lithium's effects, in apoptotic signaling induced by intrinsic and extrinsic oxidative stress. © 2005 Lippincott Williams & Wilkins.

Kirby ML, Barlow RL, Bloomquist JR. 2001. Neurotoxicity of the organochlorine insecticide heptachlor to murine striatal dopaminergic pathways. Toxicol Sci 61(1):100-106.
Abstract: Changes in biochemical status of nerve terminals in the corpus striatum, one of the primary brain regions affected in Parkinson's disease, were studied in groups of C57BL/6 mice treated by ip injection three times over a 2-week period with 3-100 mg/kg heptachlor. On average, the maximal rate of striatal dopamine uptake increased > 2-fold in mice treated at doses of 6 mg/kg heptachlor and 1.7-fold at 12 mg/kg heptachlor, Increases in maximal rate of striatal dopamine uptake were attributed to induction of the dopamine transporter (DAT) and a compensatory response to elevated synaptic levels of dopamine. Significant increase in V-max of striatal DAT was not observed at doses > 12 mgnig, which suggested that toxic effects of heptachlor epoxide may be responsible for loss of maximal dopamine uptake observed at higher doses of heptachlor. In support of this conclusion, polarigraphic measurements of basal synaptosomal respiration rates from mice treated with doses of heptachlor > 25 mg/kg indicated marked, dose-dependent depression of basal tissue;respiration, At doses of 6 and 12 mg/kg heptachlor, which increased expression of striatal DAT, uptake of 5-hydroxytryptamine into cortical synaptosomes was unaffected. Thus, striatal dopaminergic nerve terminals were found to be differentially sensitive to heptachlor. This reduced sensitivity of serotonergic pathways was mirrored in the greater potency of heptachlor epoxide to cause release of dopamine from preloaded striatal synaptosomes in vitro compared to release of serotonin from cortical membranes. These results suggest that heptachlor, and perhaps other organochlorine insecticides, exert selective effects on striatal dopaminergic neurons and may play a role in the etiology of

idiopathic Parkinson's disease.

Kirby ML, Barlow RL, Bloomquist JR. 2002. Selective effects of cyclodiene insecticides on dopamine release in mammalian synaptosomes. Toxicol Appl Pharmacol 181(2):89-92.

Kirby ML, Castagnoli K, Bloomquist JR. 1999. In vivo effects of deltamethrin on dopamine neurochemistry and the role of augmented neurotransmitter release. Pestic Biochem Physiol 65(3):160-168.
Abstract: Neurochemical analyses of dopamine, consistent with the development of parkinsonism, were performed in C57BL6 male mice. Mice were treated by intraperitoneal injection, three times over a 2-week period with 6 mg/kg deltamethrin alone or in combination with a single treatment of 20 mg/kg of the parkinsonian neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In ex vivo synaptosomes prepared from treated mice, deltamethrin caused a 70% increase in maximal dopamine uptake, which would be consistent with increased dopamine outflow in vivo and suggested an up-regulation in dopamine transporter expression. In contrast, MPTP treatment had little effect on dopamine transport but it reversed the deltamethrin-induced increase in V-max when given in combination. potent effects of deltamethrin on dopamine release were confirmed in vitro, where deltamethrin had an EC50 of 48 nM for enhancing veratridine-stimulated dopamine release from preloaded striatal synaptosomes. Under similar experimental conditions. deltamethrin had an EC50 for enhancing glutamate release of 412 nM and an EC50 for enhancing serotonin release of 117 nM. Thus, the dopaminergic nerve terminals of the striatum were more sensitive to pyrethroid than those of other neurotransmitter types, and loss of dopamine from striatal terminals is a cardinal sign of Parkinson's disease. The augmented release of dopamine and glutamate in vivo could underlie deltamethrin-induced neuronal insult, since elevated levels of these neurotransmitters are known to be neurotoxic. However, at the dose and assessment times used in this study, dopamine and DOPAC levels were not significantly affected by deltamethrin, although there was a small increase in the metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), consistent with increased turnover of dopamine in vivo. In accord with previous studies, MPTP alone decreased levels of both dopamine and DOPAC. When co-applied, MPTP reversed the small increase in DOPAC caused by deltamethrin, perhaps indicating greater toxicity in the double-treatment group. Higher doses or longer exposure times would be expected to yield greater effects of deltamethrin on dopamine content in the nigrostriatum. (C) 1999 Academic Press.

Kitamura Y, Inden M, Miyamura A, Kakimura J, Taniguchi T, Shimohama S. 2002. Possible involvement of both mitochondria- and endoplasmic reticulum-dependent caspase pathways in rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells. Neurosci Lett 333(1):25-28.
Abstract: Recently, it has been shown that rotenone, a specific inhibitor of mitochondrial complex 1, is a useful tool in animal models of Parkinson's disease, but the mechanism of rotenone-induced neuronal death is not fully understood. In human neuroblastoma SH-SY5Y cells, rotenone induced the

degradation of procaspases-12, -9 and -3, followed by cleavage of poly (adenosine diphosphate-ribose) polymerase, DNA fragmentation and cell death. Pretreatment with phorbol-12-myristate-13-acetate inhibited the rotenone-induced decrease in procaspases-9 and -3, but not that in procaspase-12. In contrast, benzyloxycarbonyl-Val-Ala-Asp(OCH3)-CH2F inhibited the decrease in procaspase-12, but not those in procaspases-9 and -3 in this study. These results suggest that rotenone may induce activation of both mitochondria- and endoplasmic reticulum-dependent caspases in human SH-SY5Y cells. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Kitamura Y, Inden M, Sanada H, Takata K, Taniguchi T, Shimohama S, Orii H, Mochii M, Agata K, Watanabe K. 2003. Inhibitory effects of antiparkinsonian drugs and caspase inhibitors in a parkinsonian flatworm model. Journal of Pharmacological Sciences 92(2):137-142.
Abstract: It has been known that rotenone and 1-methyl-4-phenylpyridinium ion (MPP+, a metabolite of MPTP), which inhibit mitochondrial complex I, are useful tools for parkinsonian models in vertebrates such as primates and rodents. Planarian, an invertebrate flatworm, has a high potential for regeneration, and dopamine plays a key role in its behavior. In the present study, we examined a cloned planarian, the GI strain from Dugesia japonica. Planarians that were treated with rotenone or MPTP underwent autolysis and individual death in a concentration and time-dependent manner. In addition, these effects induced by rotenone or MPTP were inhibited by several antiparkinsonian drugs and caspase inhibitors. These results suggest that the degeneration of planarian dopaminergic system induced by rotenone or MPTP may be mediated through caspase-like activation.

Kitazawa M, Anantharam V, Kanthasamy A, Kanthasamy AG. 2004. Dieldrin promotes proteolytic cleavage of poly(ADP-Ribose) polymerase and apoptosis in dopaminergic cells: Protective effect of mitochondrial anti-apoptotic protein Bcl-2. Neurotoxicology 25(4):589-598.
Abstract: Previously, we demonstrated that the organochlorine pesticide dieldrin induces mitochondrial depolarization, caspase-3 activation and apoptosis in dopaminergic PC12 cells. We also demonstrated that protein kinase Cdelta (PKCdelta), a member of a novel PKC family of proteins, is proteolytically activated by caspase-3 to mediate apoptotic cell death processes. In the present study, we have further characterized the protective effect of the major mitochondrial anti-apoptotic protein Bcl-2 against dieldrin-induced apoptotic events in dopaminergic cells. Exposure to dieldrin (30-100 muM) produced significant cytotoxicity and caspase-3 activation within 3 h in vector-transfected PC12 cells, whereas human Bcl-2-transfected PC12 cells were almost completely resistant to dieldrin-induced cytotoxicity and caspase-3 activation. Also, dieldrin (30-300 muM) treatment induced proteolytic cleavage of poly(ADP-ribose) polymerase (PARP), which was blocked by pretreatment with caspase-3 inhibitors Z-DEVD-FMK and Z-VAD-FMK. Additionally, dieldrin-induced chromatin condensation and DNA fragmentation were completely blocked in Bcl-2-overexpressed PC12 cells as compared to vector control cells. Together,

these results clearly indicate that overexpression of mitochondrial anti-apoptotic protein protects against dieldrin-induced apoptotic cell death and further suggest that dieldrin primarily alters mitochondrial function to initiate apoptotic cell death in dopaminergic cells. (C) 2003 Elsevier Inc. All rights reserved.

Kitazawa M, Anantharam V, Kanthasamy AG. 2001. Dieldrin-induced oxidative stress and neurochemical changes contribute to apoptotic cell death in dopaminergic cells. Free Radic Biol Med 31(11):1473-1485.
Abstract: We examined the acute toxicity of dieldrin, a possible environmental risk factor of Parkinson's disease, in a dopaminergic cell model, PC12 cells, to determine early cellular events underlying the pesticide-induced degenerative processes. EC50 for 1 h dieldrin exposure was 143 muM for PC12 cells, whereas EC50 for non-dopaminergic cells was 292-351 muM, indicating that dieldrin is more toxic to dopaminergic cells. Dieldrin also induced rapid, dose-dependent releases of dopamine and its metabolite, DOPAC, resulting in depletion of intracellular dopamine. Additionally, dieldrin exposure caused depolarization of mitochondrial membrane potential in a dose-dependent manner. Flow cytometric analysis showed generation of reactive oxygen species (ROS) within 5 min of dieldrin treatment, and significant increases in lipid peroxidation were also detected following 1 h exposure. ROS generation was remarkably inhibited in the presence of SOD. Dieldrin-induced apoptosis was significantly attenuated by both SOD and MnTBAP (SOD mimetic), suggesting that dieldrin-induced superoxide radicals serve as important signals in initiation of apoptosis. Furthermore, pretreatment with deprenyl (MAO-inhibitor) or alpha -methyl-L-p-tyro sine (TH-inhibitor) also suppressed dieldrin-induced ROS generation and DNA fragmentation. Taken together, these results suggest that rapid release of dopamine and generation of ROS are early cellular events that may account for dieldrin-induced apoptotic cell death in dopaminergic cells. (C) 2001 Elsevier Science Inc.

Kitazawa M, Anantharam V, Kanthasamy AG. 2003. Dieldrin induces apoptosis by promoting caspase-3-dependent proteolytic cleavage of protein kinase C delta in dopaminergic cells: Relevance to oxidative stress and dopaminergic degeneration. Neuroscience 119(4):945-964.
Abstract: We previously reported that dieldrin, one of the potential environmental risk factors for development of Parkinson's disease, induces apoptosis in dopaminergic cells by generating oxidative stress. Here, we demonstrate that the caspase-3-dependent proteolytic activation of protein kinase Cdelta (PKCdelta) mediates as well as regulates the dieldrin-induced apoptotic cascade in dopaminergic cells. Exposure of PC12 cells to dieldrin (100-300 muM) results in the rapid release of cytochrome C, followed by the activation of caspase-9 and caspase-3 in a time- and dose-dependent manner. The superoxide dismutase mimetic Mn(III)tetrakis(4-benzoic acid) porphyrin chloride significantly attenuates dieldrin-induced cytochrome C release, indicating that reactive oxygen species may contribute to the activation of pro-apoptotic factors. Interestingly, dieldrin proteolytically cleaves native PKCdelta into a 41 kDa catalytic subunit and a 38 kDa regulatory subunit to activate the kinase. The dieldrin-induced proteolytic

cleavage of PKCdelta and induction of kinase activity are completely inhibited by pretreatment with 50-100 muM concentrations of the caspase inhibitors benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone (Z-VAD-FMK) and benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethylketone (Z-DEVD-FMK), indicating that the proteolytic activation of PKCdelta is caspase-3-dependent. Additionally, Z-VAD-FMK, Z-DEVD-FMK or the PKCdelta specific inhibitor rottlerin almost completely block dieldrin-induced DNA fragmentation. Because dieldrin dramatically increases (40-80-fold) caspase-3 activity, we examined whether proteolytically activated PKCdelta amplifies caspase-3 via positive feedback activation. The PKC8 inhibitor rottlerin (3-20 muM) dose-dependently attenuates dieldrin-induced caspase-3 activity, suggesting positive feedback activation of caspase-3 by PKCdelta. Indeed, delivery of catalytically active recombinant PKCdelta via a protein delivery system significantly activates caspase-3 in PC12 cells. Finally, overexpression of the kinase-inactive PKCdelta(K376R) mutant in rat mesencephalic dopaminergic neuronal cells attenuates dieldrin-induced caspase-3 activity and DNA fragmentation, further confirming the pro-apoptotic function of PKCdelta in dopaminergic cells. Together, we conclude that caspase-3-dependent proteolytic activation of PKCdelta is a critical event in dieldrin-induced apoptotic cell death in dopaminergic cells. (C) 2003 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Klodowska-Duda G, Jasinska-Myga B, Safranow K, Boczarska-Jedynak M, Opala G. 2005 Nov-Dec. [The role of environmental factors in Parkinson's disease may depend on disease onset age.]. Neurol Neurochir Pol 39(6):445-50. Abstract: Background and purpose: Various factors are suspected to participate in PD onset and include environment-related factors and workplace exposure to pesticides, metals and hydrocarbons. Nevertheless, results of epidemiological research are inconsistent. Some authors emphasize hydrocarbons exposure to younger patients. Our aim was to compare PD risk factors to onset age. Material and methods: Of 174 patients with idiopathic PD, without dementia, two subgroups were isolated: 65 patients with early onset PD (EOPD) below 50 (n=65, age 52.8+/-7.6 years, onset 42.8+/-5.3 years) and 109 patients with late onset (LOPD) above 50 (n=109, age 67.8+/-7.0, onset 60.8+/-6.7 years). Various environmental factors reported in literature were analyzed. Results: The univariate analysis showed that factors significantly predisposing to EOPD are vocational education (OR 3.24, 95%CI 1.50-7.00, p<0.003), smoking (OR 1.94, 95%CI 1.02-3.69, p<0.05), well water consumption at 20-40 (OR 2.77, 95%CI 1.31-5.86, p<0.008), and after 40 (OR 4.84, 95%CI 1.95-11.99, p<0.0007), side-effects following exposure to paints (OR 2.26, 95%CI 1.10-4.66, p<0.03) and exposure to solvents (OR 1.98, 95%CI 0.96-4.07, p<0.07) on borderline significance. Drinking well water both between 20-40 and after 40 involved a substantial increase in EOPD (OR 6.57, 95%CI 2.43-17.75, p<0.0002). Education only at a primary level proved to be protective against EOPD (OR 0.20, 95%CI 0.07-0.55, p<0.002). The multivariate logistic regression model demonstrated that independent EOPD risk factors are smoking (OR 2.20, 95%CI 1.07-4.53, p<0.04) and well water consumption both between 20-40 and after 40 (OR

8.29, 95%CI 2.73-25.23, p<0.0002), whilst the independent protective factor is education only at a primary level (OR 0.17, 95%CI 0.05-0.53, p<0.003). Conclusions: Our research demonstrated that a number of independent environmental factors significantly affect the risk of PD onset at younger ages. Presumably, some of the observed differences in the results of research of various authors into PD risk factors may be caused by ignoring onset age within the researched patients.

Koldkjaer OG, Wermuth L, Bjerregaard P. 2004. Parkinson's disease among Inuit in Greenland: organochlorines as risk factors. Int J Circumpolar Health 63 Suppl 2:366-8.
Abstract: OBJECTIVES: In the present study we investigate organochlorines as possible risk factors for Parkinson's disease (PD) in an arctic population. This has never been done before. STUDY DESIGN: Case-control study of Inuit in Greenland. MATERIALS AND METHODS: Plasma from 31 PD (20 males and 11 females) (mean age 69 yr) and 122 controls (57 males and 65 females) (mean age 61 yr) was analysed for 31 PCBs and pesticides by dual-column GC-ECD and GC-NCI/MS. RESULTS: Plasma concentrations of PCBs and pesticides were markedly increased in both PD and controls. The concentrations did not differ between the PD cases and controls. However, the mean DDE concentration was higher in PD than in controls (42.1 and 15.0 microg/l, respectively, and with a wide range among the PD cases). The difference was significant for log transformed DDE values after control for age and sex (p=0.005). CONCLUSION: A few epidemiological studies indicate a possible connection between exposure to pesticides and PD. The idea that exposure to organochlorines may be an important risk factor for PD among the Inuit in Greenland requires more investigations.

Koller W, Vetere-Overfield B, Gray C, Alexander C, Chin T, Dolezal J, Hassanein R, Tanner C. 1990 Aug. Environmental risk factors in Parkinson's disease. Neurology 40(8):1218-21.
Abstract: To investigate possible risk factors for Parkinson's disease (PD) we conducted a case-control study of 150 PD patients and 150 age- and sex-matched controls. We interviewed and examined all 300 subjects. We collected demographic data including lifetime histories of places of residence, source of drinking water, and occupations such as farming. Subjects completed a detailed questionnaire regarding herbicide/pesticide exposure. Rural living and drinking well water were significantly increased in the PD patients. This was observed regardless of age at disease onset. Drinking well water was dependent on rural living. There were no significant differences between cases and controls for farming or any measure of exposure to herbicides or pesticides. These data provide further evidence that an environmental toxin could be involved in the etiology of PD.

Koller WC. 1986. Paraquat and parkinsons-disease. Neurology 36(8):1147.

Koller WC. 1987. Paraquat and parkinsons-disease - reply. Neurology 37(4):728.

Kotake Y, Ohta S. 2003. MPP plus analogs acting on mitochondria and inducing neuro-degeneration. Curr Med Chem 10(23):2507-2516.
Abstract: This review focuses on the mechanisms of action and the injurious effect of complex I inhibitors, of which 1-methyl-4-phenylpyridinium ion (MPP+) is a well studied example. These compounds can be divided into two groups, i.e. competitive inhibitors with respect to ubiquinone, such as piericidine A, and noncompetitive inhibitors such as rotenone. Complex I inhibitors such as MPP+ have been reported to induce anatomical, behavioral, and biochemical changes similar to those seen in Parkinson's disease, which is characterized by nigrostriatal dopaminergic neuro-degeneration. Spectroscopic analyses and structure-activity relationship studies have indicated that the V-shaped structure of the rotenone molecule is critical for binding to the rotenone binding site on complex I. Many isoquinoline derivatives, some of them endogenous, are also complex I inhibitors. Many lines of evidence show that complex I inhibitors elicit neuronal cell death. Recently, it was reported that chronic and systemic exposure to low-dose rotenone reproduces the features of Parkinson's disease. This work further focused attention on compounds acting on mitochondria, such as MPP+. In Guadeloupe, the French West Indies, patients with atypical parkinsonism or progressive supranuclear palsy are frequently encountered. These diseases seem to be associated with ingestion of tropical herbal teas or tropical fruits of the Annonaceae family, which contain complex I inhibitors such as benzylisoquinoline derivatives and acetogenins. Complex I inhibitors may not simply result in reactive oxygen species generation or ATP exhaustion, but may influence complex downstream signal transduction processes. An understanding of these changes would throw light on the ways in which complex I inhibitors induce a wide range of abnormalities.

Kotake Y, Taguchi R, Okuda K, Sekiya Y, Tasaki Y, Hirobe M, Ohta S. 2005. Neuroprotective effect of 1-methyl-1,2,3,4-tetrahydroisoquinoline on cultured rat mesencephalic neurons in the presence or absence of various neurotoxins. Brain Res 1033(2):143-150.
Abstract: 1-Methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) is an endogenous brain amine and its content in parkinsonian brain is decreased compared with that in control brain. There is some evidence that 1MeTIQ protects dopaminergic neurons against dysfunction such as that seen in Parkinson's disease. In this study, we examined the neuroprotective effect of 1MeTIQ against four dopaminergic neurotoxins, 1-methyl-4-phenylpyridinuim ion, 6-hydroxydopamine, rotenone, and 1-benzyl-1,2,3,4-tetrahydroisoquinoline, in cultured rat mesencephalic neurons. 1MeTIQ exerted neuroprotective action against all these toxins. Furthermore, (R)-1MeTIQ was neuroprotective, while (S)-1MeTIQ had little effect, indicating that the effect is stereoselective. The protective action of 1MeTIQ was most effective in mesencephalic neurons, especially in tyrosine hydroxylase-positive neurons. 1MeTIQ showed no affinity for dopamine receptors and did not influence the inhibition of mitochondrial respiratory complex I by rotenone, 1-methyl-4-phenylpyridinuim ion, or 1-benzyl-1,2,3,4-tetrahydroisoquinoline. These results raise the possibility

that 1MeTIQ indirectly acts as an anti-oxidant such as the induction of anti-oxidative enzymes, because all these four neurotoxins can burden oxidative stress in common. This is the first report to confirm a protective effect of 1MeTIQ at the cultured neuron level, and it may have potential as a lead compound for the development of new agents to treat Parkinson's disease. (C) 2005 Elsevier B.V All rights reserved.

Kress GJ, Reynolds IJ. 2005. Dopaminergic neurotoxins require excitotoxic stimulation in organotypic cultures. Neurobiol Dis 20(3):639-645.
Abstract: We have investigated the properties of the dopaminergic neurotoxins 6-hydroxydopamine, 1-methyl-4-phenylpyridinium and rotenone using an organotypic culture that included slices of substantia nigra, striatum and cortex maintained for about 20 days in vitro. At this age, the organotypic culture contains dopaminergic neurons, visualized using tyrosine hydroxylase (TH) immunohistochemistry, that project into the striatal slice and extend up to 1 mm into the cortical slice. Using TH immunohistochemistry to assess survival of dopaminergic neurons, we found that the three dopaminergic toxins alone were not selectively neurotoxic. However, the addition of a low concentration of N-methyl-D-aspartate together with each individual toxin resulted in profound injury to the dopamnergic neurons, reflected by the loss of cell bodies and the fragmentation of processes. The combined toxicity was completely blocked by MK801. To assess the specificity of the injury, we measured the diameter of cell nuclei in the organotypic culture stained with Hoechst 33342 because the nucleus shrinks when neurons are injured. These measurements showed that the combined toxin treatment selectively injured only the TH immunoreactive cells. Thus, in a model culture system where dopaminergic neurons innervate appropriate targets, excitotoxicity appears to be essential for the manifestation of the toxic actions of 6-hydroxydopamine, 1-methyl-4-phenylpyridinium and rotenone. (c) 2005 Elsevier Inc. All rights reserved.

Ku MC, Huang CC, Kuo HC, Yen TC, Chen CJ, Shih TS, Chang HY. 2003. Diffuse white matter lesions in carbon disulfide intoxication: Microangiopathy or demyelination. Eur Neurol 50(4):220-224.
Abstract: Long-term exposure to carbon disulfide (CS2) may induce diffuse encephalopathy with parkinsonism, pyramidal signs, cerebellar ataxia, and cognitive impairments, as well as axonal polyneuropathy. The pathogenic mechanisms of diffuse encephalopathy are unclear, although vasculopathy and toxic demyelination have been proposed. Recently, we have encountered a patient who developed headache, limb tremors, gait disturbance, dysarthria, memory impairment, and emotional lability after long-term exposure to CS2. The brain magnetic resonance images (MRI) showed diffuse hyperintensity lesions in T-2-weighted images in the subcortical white matter, basal ganglia, and brain stem. The brain computed tomography perfusion study revealed a diffusely decreased regional cerebral blood flow and prolonged regional mean transit time in the subcortical white matter and basal ganglion. To our knowledge, there have been few reports demonstrating diffuse white matter lesions in chronic CS2 encephalopathy using brain MRI. In addition, the Tc-99m-

TRODAT-1 single photon emission computed tomography showed a normal uptake of the dopamine transporter, indicating a normal presynaptic dopaminergic pathway. We conclude that diffuse white matter lesions may develop after chronic exposure to CS2, possibly through microangiopathy. In addition, CS2 poisoning can be considered as one of the causes of chronic leukoencephalopathy.

Kuopio AM, Marttila RJ, Helenius H, Rinne UK . 1999. Environmental risk factors in Parkinson's disease. Mov Disord 14(6):928-939.
Abstract: We studied the environmental risk factors of Parkinson's disease (PD) in Finland, particularly those related to rural environment, in a prevalence material in 1992. The population numbered 196,864 people, including urban and rural areas. In this community-based study, we used a case-control method with personal investigation of the case subjects (n = 123) and matched control subjects (n = 246). Analyses were carried out by conditional logistic regression model. Case subjects had far fewer domestic animals at home during their lifetime, including cows, sheep, pigs, and chickens. The difference was even more obvious in those under the age of 20 years, including also cats and horses, but diminished after 20 years. The number of different animal species was smaller with case subjects as was the duration of animal contacts. Case subjects found their work physically heavier and exercised more. The mean age at onset in ever-smoking men was significantly higher than in never-smoking men. No special reason for nonsmoking increased, and a physical reason decreased the risk of PD. Area of birth or living, farming and other occupations, types of drinking water, pesticide and herbicide use, head injuries, use of alcohol, education, and carbon monoxide poisonings were similar among case subjects and control subjects. In conclusion, domestic animals, or something that is connected with the animals, may have a protecting effect against PD. Alternatively, the observed negative associations of domestic animals at home and subsequent PD may only be a marker of other environmental conditions or lifestyles.

Kventsel I, Berkovitch M, Reiss A, Bulkowstein M, Kozer E. 2005. Scopolamine treatment for severe extra-pyramidal signs following organophosphate (chlorpyrifos) ingestion. Clin Toxicol 43(7):877-879.
Abstract: Background. The use of competitive inhibitors of acetylcholine other than atropine, for patients with organophosphate poisoning, is controversial. Because scopolamine ability to cross the blood-brain barrier is better than that of atropine, it has been suggested that it should be used in patients with organophosphate poisoning who have central nervous system manifestations. Case Description. A 17-year-old girl was admitted to the pediatric ward after ingesting chlorpyrifos as a suicidal attempt. She reported vomiting three times. She had no other symptoms for 12 hours and then over the course of 36 hours gradually developed extra-pyramidal signs and became comatose. She was treated with intravenous scopolamine. Within 3 minutes the patient started to respond to verbal commands and answered simple questions, rigidity subsided, and she was able to sit in bed. She was discharged after 4 days with no neurological sequelae. Conclusions. We suggest, that in patients with organophosphate

poisoning who have mainly central nervous system toxicity, scopolamine administration might be considered.

Kweon GR, Marks JD, Krencik R, Leung EH, Schumacker PT, Hyland K, Kang UJ. 2004. Distinct mechanisms of neurodegeneration induced by chronic complex I inhibition in dopaminergic and non-dopaminergic cells. J Biol Chem 279(50):51783-51792.
Abstract: Chronic mitochondrial dysfunction, in particular of complex I, has been strongly implicated in the dopaminergic neurodegeneration in Parkinson's disease. To elucidate the mechanisms of chronic complex I disruption-induced neurodegeneration, we induced differentiation of immortalized midbrain dopaminergic (MN9D) and non-dopaminergic (MN9X) neuronal cells, to maintain them in culture without significant cell proliferation and compared their survivals following chronic exposure to nanomolar rotenone, an irreversible complex I inhibitor. Rotenone killed more dopaminergic MN9D cells than non-dopaminergic MN9X cells. Oxidative stress played an important role in rotenone-induced neurodegeneration of MN9X cells, but not MN9D cells: rotenone oxidatively modified proteins more in MN9X cells than in MN9D cells and antioxidants decreased rotenone toxicity only in MN9X cells. MN9X cells were also more sensitive to exogenous oxidants than MN9D cells. In contrast, disruption of bioenergetics played a more important role in MN9D cells: rotenone decreased mitochondrial membrane protential and ATP levels in MN9D cells more than in MN9X cells. Supplementation of cellular energy with a ketone body, D-beta-hydroxybutyrate, decreased rotenone toxicity in MN9D cells, but not in MN9X cells. MN9D cells were also more susceptible to disruption of oxidative phosphorylation or glycolysis than MN9X cells. These findings indicate that, during chronic rotenone exposure, MN9D cells die primarily through mitochondrial energy disruption, whereas MN9X cells die primarily via oxidative stress. Thus, intrinsic properties of individual cell types play important roles in determining the predominant mechanism of complex I inhibition-induced neurodegeneration.

Lai BCL, Marion SA, Teschke K, Tsui JKC. 2002. Occupational and environmental risk factors for Parkinson's disease. Parkinsonism & Related Disorders 8 (5):297-309.
Abstract: The etiology of Parkinson's disease (PD) remains obscure. Current research suggests that a variety of occupational and environmental risk factors may be linked to PD. This paper provides an overview of major occupational and environmental factors that have been associated with the development of PD and tries to assess current thinking about these factors and their possible mechanisms of operation. While clear links to rural living, dietary factors, exposure to metals, head injury, and exposure to infectious diseases during childhood have not been established, there is general agreement that smoking and exposure to pesticides affect the probability of developing PD. (C) 2002 Elsevier Science Ltd. All rights reserved.

Lalonde FM, Myslobodsky M. 2003 Aug. Are dopamine antagonists a risk factor for breast cancer? An answer from Parkinson's disease. Breast 12(4):

280-2.
Abstract: Women undergoing chemotherapy for breast cancer are often administered dopamine antagonist adjuvant medications that may increase levels of prolactin potentially increasing the risk of cancer. Using nationwide computerized registers of death data for the years 1991 through 1996 we examined 12,430,473 deaths of persons over 40 years of age and extracted 144,364 cases with Parkinson's disease (PD), a dopamine deficient population. Patients with PD had lower rates of breast and other types of malignancies, even in the presence of depression and suicide.

Lamango NS. 2005. Liver prenylated methylated protein methyl esterase is an organophosphate-sensitive enzyme. J Biochem Mol Toxicol 19(5):347-357.
Abstract: Prenylation and subsequent methylation are essential modifications on a significant proportion of eucaryotic proteins. Proteins such as the G-gamma subunits of G-protein coupled receptors, nuclear lamins, and guanine nucleotide-binding proteins such as Ras are prenylated and undergo methylation. Prenylated methylated protein methyl esterase (PMPMEase) readily hydrolyses the prenylated protein methyl esters, thus making this step reversible and possibly regulatory. Benzoyl-glycyl-farnesyl-cysteine methyl ester (BzGFCM) was developed as a specific PMPMEase substrate and characterized by electron spray ionization mass spectrometry (ESI-MS) to be of the calculated molecular mass. Rat liver and brain PMPMEase hydrolyzed BzGFCM, forming benzoyl-glycyl-farnesyl-cysteine (BzGFC) in a time- and concentration-dependent manner. Both enzymes cleaved BzGFCM with K-m values of 4.58 +/- 0.30 and 25.57 +/- 2.36 mu M and V-max values of 2.21 +/- 0.03 and 0.17 +/- 0.003 nmol/ min/mg, respectively. The liver enzyme eluted from a gel-filtration column as a single peak of apparent size, 89 kDa. The brain enzyme eluted as two main peaks of 53 and 890 kDa. Organophosphorus pesticides (OPs), which are suspected to be involved in human disorders such as parkinsonism, neuronal, and retinal degeneration, inhibited the liver enzyme with IC50 values from 4.77 mu M for parathion to 0.04 mu M for paraoxon, respectively. Only about 25% of the brain enzyme was inhibited by 0.5-1 mM solutions of mipafox, while 0.1 and 1 mM paraoxon inhibited over 50% and 95% of the enzyme, respectively. Paraoxon is thus about 2250 times less potent against the brain than the liver PMPMEase. BzGFCM was not hydrolyzed by various cholinesterases, indicating its specificity for PMPMEase. Perturbations in prenylated protein metabolism might play a role in noncholinergic OPs-induced toxicity, since prenylated proteins play such important roles in cell signaling, proliferation, differentiation, and apoptosis. (c) 2005 Wiley Periodicals, Inc.

Lamensdorf I, Eisenhofer G, Harvey-White J, Nechustan A, Kirk K, Kopin IJ. 2000. 3,4-Dihydroxyphenylacetaldehyde potentiates the toxic effects of metabolic stress in PC12 cells. Brain Res 868( 2):191-201.
Abstract: 3,4-Dihydroxyphenylacetaldehyde (DOPAL) is a toxic metabolite formed by the oxidative deamination of dopamine. This aldehyde is mainly oxidized to 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase (ALDH), but is also partly reduced to 3,4-

dihydroxyphenylethanol (DOPET) by aldehyde or aldose reductase (ARs). In a previous study, we found that rotenone, a complex I inhibitor, induced a rapid accumulation of DOPAL and DOPET in the medium of cultured PC12 cells. Here, we examined the potential role of DOPAL in the toxicity induced by complex I inhibition in PC12 cells and compared the effects of rotenone on concentrations of DOPAL and DOPET to those of MPP+. DOPAL and DOPET levels were increased by rotenone but decreased by MPP+. Inhibition of ALDH by daidzein reduced the formation of DOPAC and increased the accumulation of DOPAL. Inhibition of ARs (with AL1576) diminished DOPET formation and elevated DOPAL concentrations. Combined inhibition of ALDH and ARs markedly elevated DOPAL concentrations while diminishing DOPET and DOPAC levels. The elevation of DOPAL levels induced by combined inhibition of ALDH and ARs had no effect on cell viability. However, combined inhibition of ALDH and ARs potentiated rotenone-induced toxicity. Both the potentiation of toxicity and, the increase in DOPAL levels were blocked by inhibition of monoamine oxidase with clorgyline indicating that accumulation of DOPAL was responsible for the potentiated rotenone-induced toxicity following combined inhibition of ALDH and ARs. Since complex I dysfunction is reported to be involved in the pathogenesis of Parkinson's disease, DOPAL potentiation of the deleterious effects of complex I inhibition may contribute to the specific vulnerability of dopaminergic neurons to injury. 

Landrigan PJ, Sonawane B, Butler RN, Trasande L, Callan R, Droller D. 2005. Early environmental origins of neurodegenerative disease in later life. Environ Health Perspect 113(9):1230-1233.
Abstract: Parkinson disease (PD) and Alzheimer disease (AD), the two most common neurodegenerative disorders in American adults, are of purely genetic origin in a minority of cases and appear in most instances to arise through interactions among genetic and environmental factors. In this article we hypothesize that environmental exposures in early life may be of particular etiologic importance and review evidence for the early environmental origins of neurodegeneration. For PD the first recognized environmental cause, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), was identified in epidemiologic studies of drug abusers. Chemicals experimentally linked to PD include the insecticide rotenone and the herbicides paraquat and maneb; interaction has been observed between paraquat and maneb. In epidemiologic studies, manganese has been linked to parkinsonism. In dementia, lead is associated with increased risk in chronically exposed workers. Exposures of children in early life to lead, polychlorinated biphenyls, and methylmercury have been followed by persistent decrements in intelligence that may presage dementia. To discover new environmental causes of AD and PD, and to characterize relevant gene-environment interactions, we recommend that a large, prospective genetic and epidemiologic study be undertaken that will follow thousands of children from conception (or before) to old age. Additional approaches to etiologic discovery include establishing incidence registries for AD and PD,

conducting targeted investigations in high-risk populations, and improving testing of the potential neurologic toxicity of chemicals.

Langston JW. 1998. Epidemiology versus generics in Parkinson's disease: Progress in resolving an age-old debate. Ann Neurol 44(3):S45-S52.
Abstract: Determining the relative contributions of environment and heredity to the cause of Parkinson's disease (PD) is more than an academic issue because its resolution dictates future research directions to an enormous degree. This article reviews new advances on both sides of this equation. The recent identification of the genetic mutation responsible for parkinsonism in a large Italian kindred is likely to provide exciting new research opportunities but the mutation does not appear to be responsible for the vast majority of PD. A large twin study also points away from genetic influences as important, at least in patients with disease beginning after the age of 50 years. On the other hand, genetic influences loom large in younger-onset disease. With regard to the environment, epidemiologic studies have provided only broad, thought-tantalizing clues to the cause of the disease. Although rural living, well-water consumption, and exposure to pesticides have emerged as potential risk factors, identification of specific agents is lacking, and aging remains as the only unequivocal risk factor for the disease. The surprisingly strong inverse relationship between cigarette smoking and PD provides an intriguing lead, but novel experimental avenues to pursue this observation are not readily obvious. The amyotrophic lateral sclerosis/dementia/parkinsonism complex in the western Pacific suggests the possibility of long-latency toxins, but pinning down a specific causative agent for this syndrome has eluded investigators to date. Despite the many obstacles ahead, however, research on PD appears to be more robust than ever, and our quest to find its cause appears to be under a full head of steam as we approach the 21st century.

Lannuzel A, Michel PP, Hoglinger GU, Champy P, Jousset A, Medja F, Lombes A, Darios F, Gleye C, Laurens A, Hocquemiller R, Hirsch EC, Ruberg M. 2003. The mitochondrial complex I inhibitor annonacin is toxic to mesencephalic dopaminergic neurons by impairment of energy metabolism. Neuroscience 121(2):287-296.
Abstract: The death of dopaminergic neurons induced by systemic administration of mitochondrial respiratory chain complex I inhibitors such as 1-methyl-4-phenylpyridinium (MPP+; given as the prodrug 1-methyl-1,2,3,6-tetrahydropyridine) or the pesticide rotenone have raised the question as to whether this family of compounds are the cause of some forms of Parkinsonism. We have examined the neurotoxic potential of another complex I inhibitor, annonacin, the major acetogenin of Annona muricata (soursop), a tropical plant suspected to be the cause of an atypical form of Parkinson disease in the French West Indies (Guadeloupe). When added to mesencephalic cultures for 24 h, annonacin was much more potent than MPP+ (effective concentration [EC50] = 0.018 versus 1.9 muM) and as effective as rotenone (EC50 = 0.034 muM) in killing dopaminergic neurons. The uptake of [H-3]-dopamine used as an index of dopaminergic cell function was similarly reduced. Toxic effects were seen at lower concentrations when the incubation time was extended by several

days whereas withdrawal of the toxin after a short-term exposure (<6 h) arrested cell demise. Unlike MPP+ but similar to rotenone, the acetogenin also reduced the survival of non-dopaminergic neurons. Neuronal cell death was not excitotoxic and occurred independently of free radical production. Raising the concentrations of either glucose or mannose in the presence of annonacin restored to a large extent intracellular ATP synthesis and prevented neuronal cell demise. Deoxyglucose reversed the effects of both glucose and mannose. Other hexoses such as galactose and fructose were not protective. Attempts to restore oxidative phosphorylation with lactate or pyruvate failed to provide protection to dopaminergic neurons whereas idoacetate, an inhibitor of glycolysis, inhibited the survival promoting effects of glucose and mannose indicating that these two hexoses acted independently of mitochondria by stimulating glycolysis. In conclusion, our study demonstrates that annonacin promotes dopaminergic neuronal death by impairment of energy production. It also underlines the need to address its possible role in the etiology of some atypical forms of Parkinsonism in Guadeloupe. (C) 2003 IBRO. Published by Elsevier Ltd. All rights reserved.

Laplane D, Attal N, Sauron B, Debilly A, Dubois B. 1992. Lesions of basal ganglia due to disulfiram neurotoxicity. J Neurol Neurosurg Psychiatry 55(10): 925-929.
Abstract: Three cases of disulfiram induced Parkinsonism and frontal lobe-like syndrome associated with bilateral lesions of the lentiform nuclei on CT scan are reported. Symptoms developed either after an acute high dose of disulfiram (one case) or after several days to weeks of disulfiram treatment (two cases) and persisted over several years in two patients. These observations suggest that basal ganglia are one of the major targets of disulfiram neurotoxicity. The mechanisms of the lesions of basal ganglia may involve carbon disulfide toxicity.

Lapointe N, St-Hilaire M, Martinoli MG, Blanchet J, Gould P, Rouillard C, Cicchetti F. 2004. Rotenone induces non-specific central nervous system and systemic toxicity. FASEB J 18(2).
Abstract: We investigated the dopaminergic (DA) neuronal degeneration in animals subjected to systemic treatment of rotenone via subcutaneous delivery. Behavioral observations revealed a hypokinetic period in rats sacrificed at 3 and 5 days, and dystonic episodes in animals sacrificed at 8 days. Less than 20% of the total number of animals given rotenone depicted brain lesions after 8 days of treatment, as demonstrated by a significant loss of DA fibers in the striatum, but not of DA nigral neurons. Tyrosine hydroxylase-negative striatal territories were characterized by postsynaptic toxicity as demonstrated by a decreased number of interneurons labeled for choline acetyltransferase, NADPH-diaphorase, parvalbumin, and projection neurons labeled for calbindin and nerve growth factor inducible-B (NGFI-B). Post-synaptic neurodegeneration was demonstrated further by abundant striatal staining for Fluoro-Jade. Decrease in the nuclear orphan receptor Nurr1 expression was the only significant change observed at the level of the substantia nigra. Autopsy reports confirmed that animals suffered from severe digestion problems.

These data suggest that hypokinesia observed between 3 and 5 days is the result of general health problems rather than a specific motor deficit associated to Parkinson's disease (PD) symptoms. Overall, the effects of rotenone toxicity are widespread, and subcutaneous administration of this toxin does not provide the neuropathological and behavioral basis for a relevant and reliable PD model.

Lapointe N, St-Hilaire M, Martinoli MG, Blanchet J, Gould P, Rouillard C, Cicchetti F. 2004 Apr. Rotenone induces non-specific central nervous system and systemic toxicity. FASEB J 18(6):717-9.
Abstract: We investigated the dopaminergic (DA) neuronal degeneration in animals subjected to systemic treatment of rotenone via subcutaneous delivery. Behavioral observations revealed a hypokinetic period in rats sacrificed at 3 and 5 days, and dystonic episodes in animals sacrificed at 8 days. Less than 20% of the total number of animals given rotenone depicted brain lesions after 8 days of treatment, as demonstrated by a significant loss of DA fibers in the striatum, but not of DA nigral neurons. Tyrosine hydroxylase-negative striatal territories were characterized by post-synaptic toxicity as demonstrated by a decreased number of interneurons labeled for choline acetyltransferase, NADPH-diaphorase, parvalbumin, and projection neurons labeled for calbindin and nerve growth factor inducible-B (NGFI-B). Post-synaptic neurodegeneration was demonstrated further by abundant striatal staining for Fluoro-Jade. Decrease in the nuclear orphan receptor Nurr1 expression was the only significant change observed at the level of the substantia nigra. Autopsy reports confirmed that animals suffered from severe digestion problems. These data suggest that hypokinesia observed between 3 and 5 days is the result of general health problems rather than a specific motor deficit associated to Parkinson's disease (PD) symptoms. Overall, the effects of rotenone toxicity are widespread, and subcutaneous administration of this toxin does not provide the neuropathological and behavioral basis for a relevant and reliable PD model.

Laske C, Wormstall H, Einsiedler K, Buchkremer G. 2004. Alzheimer's disease with secondary Parkinson's syndrome. Case report of a patient with dementia and Parkinson's syndrome after long-term occupational exposure to insecticides, herbicides, and pesticides. Nervenarzt 75(11):1107-1111.
Abstract: This case report describes long-term occupational exposure to agricultural insecticides, herbicides, and pesticides as possible environmental risk factors of Alzheimer's disease (AD) and Parkinson's syndrome in a 59-year-old man. Initially the patient complained about disturbances in concentration, mnestic deficits, and problems finding words. In the further course of the disease, he developed Parkinson's syndrome with predominant hypokinesia and rigor in addition to mild-to-moderate dementia. Low levels of beta-amyloid 1-42 were found in the CSF Electroencephalography showed left frontotemporal theta waves. Cranial MRI revealed general brain atrophy with a maximum biparietally. In cerebral positron emission tomography, general hypometabolism was found with maxima biparietally and left frontally. The possible differential

diagnosis of AD and Parkinson's syndrome is discussed.

Latli B, Morimoto H, Williams PG, Casida JE. 1998. Photoaffinity radioligand for NADH : ubiquinone oxidoreductase: [S-(CH2)-H-3](trifluoromethyl) diazirinyl-pyridaben. Journal of Labelled Compounds & Radiopharmaceuticals 41(3):191-199.
Abstract: Pyridaben is a new and very potent insecticide and miticide that acts by inhibiting the activity of NADH:ubiquinone oxidoreductase (the most complex of all the respiratory enzymes). The binding site, presumed to be the same as that of rotenone and fenazaquin, resides at an unknown location within the 43-polypeptide-subunit Complex I. To define the structure of the pyridaben-inhibition site(s), we prepared [S-C3H2] (trifluoromethyl)diazirinylphenylacetyl as a photoaffinity probe. Tritium was incorporated by reducing 4-(trifluoromethyl)diazirinylphenylacetyl fluoride to the benzyl alcohol with freshly prepared (LiBH4)-H-3 at 97% tritium enrichment. The tritium-labeled alcohol was converted to the benzyl bromide derivative and coupled to 2-tert-butyl-4-chloro-5-mercapto-3(2H)-pyridazinone to obtain the photoaffinity probe (56 Ci/mmol) with an IC50 of 3.0 nM for NADH:ubiquinone oxidoreductase activity of bovine heart electron transport particles. [S-C3H2](Trifluoromethyl)diazirinyl-pyridaben is an improved photoaffinity radioligand combining outstanding potency for inhibiting NADH:ubiquinone oxidoreductase activity, high specific activity close to the theoretical value, and a preferred photolabile substituent (known to combine high reactivity and generation of a carbene species at wavelengths not damaging to proteins).

Le Couteur DG, Mclean AJ, Taylor MC, Woodham BL, Board PG. 1999. Pesticides and Parkinson's disease. Biomedicine & Pharmacotherapy 53(3):122-130.
Abstract: Epidemiological studies and case reports provide evidence for an association between Parkinson's disease and past exposure to pesticides. Susceptibility to the effects of pesticides and other putative neurotoxins depends on variability in xenobiotic metabolism possibly generated by genetic polymorphisms, aging and variation in exposure to environmental agents including pesticides. The simplest mechanistic hypothesis for the association of pesticides with Parkinson's disease is that pesticides or their metabolites are directly toxic to mitochondria, although modulation of xenobiotic metabolism by pesticides provides an adjunct or alternative hypothesis. (C) 1999 Elsevier, Paris.

Le Couteur DG, Muller M, Yang MC, Mellick GD, McLean AJ. 2002 Jan-Mar. Age-environment and gene-environment interactions in the pathogenesis of Parkinson's disease. Rev Environ Health 17(1):51-64.
Abstract: Parkinson's disease (PD) is a common neurodegenerative disease characterized by dopaminergic cell death and deposition of Lewy bodies within the substantia nigra of the midbrain. Although the major risk factors for PD are aging and environmental factors, there is an important genetic component. An age-related change in xenobiotic metabolism alters the metabolism of and net exposure to, environmental neurotoxins. Genetic variability in xenobiotic metabolism may similarly increase the susceptibility to PD by altering the metabolism of neurotoxins. Genetic

studies of rare familial cases of PD indicate a central mechanistic role for the aggregation of alpha-synuclein, a protein found in Lewy bodies. Environmental factors like pesticides and heavy metals can also influence alpha-synuclein aggregation. Common final pathways for aging, environmental, and genetic mechanisms can thus exist, involving both direct neurotoxicity and alpha-synuclein aggregation.

Lee HJ, Choi C, Lee SJ. 2002. Membrane-bound alpha-synuclein has a high aggregation propensity and the ability to seed the aggregation of the cytosolic form. J Biol Chem 277(1):671-678.
Abstract: alpha-Synuclein exists as at least two structural isoforms: a helix-rich, membrane-bound form and a disordered, cytosolic form. Here, we investigated the role of membrane-bound alpha-synuclein in the aggregation process. In a cell-free system consisting of isolated brain fractions, spontaneous and progressive aggregation of alpha-synuclein was observed in membranes starting at day 1, whereas no aggregation was observed in the cytosolic fraction in a 3-day period. The addition of antioxidants reduced the aggregation in the membrane fraction, implicating the role of oxidative modifications. When excess cytosolic alpha-synuclein was added to brain membranes, the rate of aggregation was increased, while the lag time was unaffected. Incorporation of cytosolic alpha-synuclein into membrane-associated aggregates was demonstrated by fractionation and co-immunoprecipitation experiments. In our recent study, we showed that mitochondrial inhibitors such as rotenone, induced alpha-synuclein aggregation in cells. In the present study using rotenone-treated cells, the earliest appearance of alpha-synuclein oligomeric species was observed in membranous compartments. Furthermore, alpha-synuclein-positive inclusions were co-stained with DiI, a membrane-partitioning fluorescent dye, confirming the presence of lipid components in alpha-synuclein aggregates. These results suggest that membrane-bound alpha-synuclein can generate nuclei that seed the aggregation of the more abundant cytosolic form.

Lee HJ, Shin SY, Choi C, Lee YH, Lee SJ. 2002. Formation and removal of alpha-synuclein aggregates in cells exposed to mitochondrial inhibitors. J Biol Chem 277(7):5411-5417.
Abstract: Mitochondrial dysfunction has been associated with Parkinson's disease. However, the role of mitochondrial defects in the formation of Lewy bodies, a pathological hallmark of Parkinson's disease has not been addressed directly. In this report, we investigated the effects of inhibitors of the mitochondria) electron-transport chain on the aggregation of alpha-synuclein, a major protein component of Lewy bodies. Treatment with rotenone, an inhibitor of complex I, resulted in an increase of detergent-resistant alpha-synuclein aggregates and a reduction in ATP level. Another inhibitor of the electron-transport chain, oligomycin, also showed temporal correlation between the formation of aggregates and ATP reduction. Microscopic analyses showed a progressive evolution of small aggregates of alpha-synuclein to a large perinuclear inclusion body. The inclusions were co-stained with ubiquitin, 20 S proteasome, gamma-tubulin, and vimentin. The perinuclear inclusion bodies, but not the small cytoplasmic

aggregates, were thioflavin S-positive, suggesting the amyloid-like conformation. Interestingly, the aggregates disappeared when the cells were replenished with inhibitor-free medium. Disappearance of aggregates coincided with the recovery of mitochondrial metabolism and was partially inhibited by proteasome inhibitors. These results suggest that the formation of alpha-synuclein inclusions could be initiated by an impaired mitochondrial function and be reversed by restoring normal mitochondrial metabolism.

Lee JM, Shih AY, Murphy TH, Johnson JA. 2003. NF-E2-related factor-2 mediates neuroprotection against mitochondrial complex I inhibitors and increased concentrations of intracellular calcium in primary cortical neurons. J Biol Chem 278(39):37948-37956.
Abstract: NF-E2-related factor-2 (Nrf2) regulates the gene expression of phase II detoxification enzymes and antioxidant proteins through an enhancer sequence referred to as the antioxidant-responsive element ( ARE). In this study, we demonstrate that Nrf2 protects neurons in mixed primary neuronal cultures containing both astrocytes (similar to 10%) and neurons (similar to 90%) through coordinate up-regulation of ARE- driven genes. Nrf2(-/-) neurons in this mixed culture system were more sensitive to mitochondrial toxin ( 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine or rotenone)-induced apoptosis compared with Nrf2(+/+) neurons. To understand the underlying mechanism of this observed differential sensitivity, we compared the gene expression profiles using oligonucleotide microarrays. Microarray data showed that Nrf2(+/+) neuronal cultures had higher expression levels of genes encoding detoxification enzymes, antioxidant proteins, calcium homeostasis proteins, growth factors, neuron-specific proteins, and signaling molecules compared with Nrf2(-/-) neuronal cultures. As predicted from the microarray data, Nrf2(-/-) neurons were indeed more vulnerable to the cytotoxic effects of ionomycin- and 2,5-di( t-butyl)-1,4-hydroquinone-induced increases in intracellular calcium. Finally, adenoviral vector-mediated overexpression of Nrf2 recovered ARE- driven gene expression in Nrf2(-/-) neuronal cultures and rescued Nrf2(+/+) neurons from rotenone- or ionomycin- induced cell death. Taken together, these findings suggest that Nrf2 plays an important role in protecting neurons from toxic insult.

Lee SJ, Youn YC, Han ES, Lee CS. 2005. Depressant effect of mitochondrial respiratory complex inhibitors on proteasome inhibitor-induced mitochondrial dysfunction and cell death in PC12 cells. Neurochem Res 30 (9):1191-1200.
Abstract: The addition of rotenone (inhibitor of respiratory complex I), 3-nitropropionic acid (complex II inhibitor), harmine (inhibitor of complexes I and II) and cyclosporin A (CsA, an inhibitor of the mitochondrial permeability transition) reduced the nuclear damage, loss in the mitochondrial transmembrane potential, cytosolic accumulation of cytochrome c, activation of caspase-3, increase in the formation of reactive oxygen species and depletion of GSH in differentiated PC12 cells treated with MG132, a proteasome inhibitor. Meanwhile, rotenone, 3-nitropropionic acid and harmine did not affect the inhibitory effect of CsA or

trifluoperazine (an inhibitor of the mitochondrial permeability transition and calmodulin antagonist) on the cytotoxicity of MG132. The results suggest that proteasome inhibition-induced mitochondrial dysfunction and cell injury may be attenuated by the inhibitions of respiratory chain complex I and II. The cytoprotective effect of the mitochondrial permeability transition prevention not appears to be modulated by respiratory complex inhibition.

Lehmensiek V, Tan EM, Schwarz J, Storch A. 2002. Expression of mutant alpha-synucleins enhances dopamine transporter-mediated MPP+ toxicity in vitro. Neuroreport 13(10):1279-1283.
Abstract: Mutations in the alpha-synuclein gene (A30P and A53T) are reported to cause familial Parkinson disease (PD), but it is not known how they result in selective dopaminergic cell death. Here we report on effects of mutant alpha-synucleins on dopamine transporter (DAT)mediated toxicity of the selective dopaminergic neurotoxin 1-methyl-4-phenylpyridinium ion (MPP+) in vitro. We established human embryonic kidney HEK-293 cell lines stably co-expressing each alpha-synuclein isoform and the human DAT. We demonstrate that expression of all alpha-synuclein isoforms enhances toxicity of general complex I inhibition (rotenone), but only the expression of mutant alpha-synucleins induces significant increased DAT-dependent toxicity of very low concentrations of MPP+ compared to wildtype protein. Proteasomal inhibition by lactacystin does not alter MPP+-toxicity in all cell lines. Our data suggest a new mechanism of MPP+-induced dopaminergic toxicity by an interaction between mutant a-synucleins and the DAT, which is independent of the function of the proteasome.

Leng A, Feldon J, Ferger B. 2003. Rotenone increases glutamate-induced dopamine release but does not affect hydroxyl-free radical formation in rat striatum. Synapse 50(3):240-250.
Abstract: Impairment of the mitochondrial complex 1 has been found in Parkinson's disease and recently long-term treatment with the complex I inhibitor rotenone led to neurodegeneration and Lewy body-like inclusions in rats. To investigate the relationship of free radical formation, complex I inhibition, and dopamine release, rotenone (15 mg/kg s.c.) was injected in male Sprague Dawley rats. Complex I inhibition was measured in the striatum and substantia nigra using the lactate accumulation assay. Dopamine release and free radical formation was determined using striatal microdialysis in combination with the salicylate hydroxylation assay. In a second experiment, glutamate (10 mM) stimulation via the microdialysis probe was used to provoke hydroxyl radical formation and dopamine release 60 min after rotenone or vehicle pretreatment. Rotenone significantly increased striatal and nigral lactate levels. However, rotenone did not produce a significant increase in hydroxyl radical formation and dopamine release, but led to a pronounced hypokinesia. In contrast, rotenone in comparison to vehicle pretreatment produced a significant augmentation of glutamate-induced dopamine release (67-fold and 31-fold increase, respectively) and did not affect the glutamate-induced hydroxyl free radical formation (23-fold and 21-fold increase, respectively). The

present study demonstrates that a single systemic rotenone administration does not lead to neurotoxicity, but rather to enhanced glutamate-induced dopamine release with no further increase of hydroxyl free radical formation. Thus, acute complex I inhibition in the presence or absence of high extracellular dopamine and glutamate levels is not critically involved in the formation of hydroxyl free radicals. (C) 2003 Wiley-Liss, Inc.

Lermontiva NN, Soliakov LS, Bachurin SO, Tkachenko SE, Serkova TP. 1989 Jun. [Evaluation of the capability of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and pyridine derivatives to evoke parkinsonism]. Biull Eksp Biol Med 107(6):699-701.
Abstract: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produce an irreversible parkinsonian-like syndrome in humans, monkeys and mice C57BL/6. Experimental parkinsonism produced by MPTP on mice C57BL/6 were studied with the aim of working up the method for testing MPTP-like substances. It has been shown that intraperitoneal administration the maximal tolerated doses of MPTP cause significant decrease (by 40-60%) of dopamine content on the mice brain. Number of injections did not influence the results. The similar administration of 4-phenyl-pyridyl and 4,4'-dipyridyl derivates, including known herbicides paraquat and cyperquat, produce neither decrease of dopamine content in the brain, nor the development of parkinsonian-like behavioral syndrome.

Li AA, Mink PJ, Mcintosh LJ, Teta MJ, Finley B. 2005. Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease. J Occup Environ Med 47(10):1059-1087.
Abstract: Exposure to pesticides may be a risk factor for developing Parkinson's disease (PD). To evaluate the evidence regarding this association in the scientific literature, we examined both analytic epidemiologic studies Of PD cases in which exposure to pesticides was queried directly and whole-animal studies for PD-like effects after systemic pesticide exposure. Epidemiologic studies were considered according to study quality parameters, and results were found to be mixed and without consistent exposure-response or Pesticide-specific patterns. These epidemiologic studies were limited by a lack of detailed and validated pesticide exposure assessment. In animal studies, no pesticide has yet demonstrated the selective set of clinical and pathologic signs that characterize human PD, particularly at levels relevant to human populations. We conclude that the animal and epidemiologic data reviewed do not provide sufficient evidence to support a causal association between pesticide exposure and PD.

Li HL, Liu DP, Liang CC. 2003. Paraoxonase gene polymorphisms, oxidative stress, and diseases. Journal of Molecular Medicine-Jmm 81(12):766-779.
Abstract: The paraoxonase (PON) gene cluster contains at least three members, including PON1, PON2, and PON3, located on chromosome 7q21.3-22.1. Until now there has been little insight into the role of the respective gene products in human physiology and pathology. However, emerging evidence from biochemical and genetic experiments is providing clues about the role(s) of the products of these genes, which indicates that

PON(s) acts as important guardians against cellular damage from toxic agents, such as organophosphates, oxidized lipids in the plasma low-density lipoproteins. In parallel, substantial data have been published on the association between the polymorphisms of PON(s) and coronary heart disease. It has become clear that the polymorphisms significantly affect the prevalence of coronary heart disease. However, the associations between the PON(s) polymorphisms and most of these conditions were found to be inconsistent when additional populations were investigated. This contribution provides an overview of the status of research of each of the three genes and the available association studies and the potential problems in interpreting the data. We also review the current evidence on the association between PON(s) polymorphisms and diseases other than coronary heart disease and some metabolic quantitative phenotypes, such as plasma lipoproteins, plasma glucose, and birthweight. Finally, we suggest directions for the future that might elucidate the role of the PON genetic polymorphisms in this potentially important function of PON(s) and the role in coronary heart disease and other related diseases.

Li J, Spletter ML, Johnson DA, Wright LS, Svendsen CN, Johnson JA. 2005. Rotenone-induced caspase 9/3-independent and -dependent cell death in undifferentiated and differentiated human neural stem cells. J Neurochem 92(3):462-476.
Abstract: We used human neural stem cells (hNSCs) and their differentiated cultures as a model system to evaluate the mechanism(s) involved in rotenone (RO)- and camptothecin (CA)-induced cytotoxicity. Results from ultrastructural damage and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining indicated that RO-induced cytotoxicity resembled CA-induced apoptosis more than H2O2-induced necrosis. However, unlike CA-induced, caspase 9/3-dependent apoptosis, there was no increased activity in caspase 9, caspase 3 or poly (ADP-ribose) polymerase (PARP) cleavage in RO-induced cytotoxicity, in spite of time-dependent release of cytochrome c and apoptosis-inducing factor (AIF) following mitochondrial membrane depolarization and a significant increase in reactive oxygen species generation. Equal doses of RO and CA used in hNSCs induced caspase 9/3-dependent apoptosis in differentiated cultures. Time-dependent ATP depletion occurred earlier and to a greater extent in RO-treated hNSCs than in CA-treated hNSCs, or differentiated cultures treated with RO or CA. In conclusion, these results represent a unique ultrastructural and molecular characterization of RO- and CA-induced cytotoxicity in hNSCs and their differentiated cultures. Intracellular ATP levels may play an important role in determining whether neural progenitors or their differentiated cells follow a caspase 9/3-dependent or -independent pathway in response to acute insults from neuronal toxicants.

Li J, Uversky VN, Fink AL. 2002. Conformational behavior of human alpha-synuclein is modulated by familial Parkinson's disease point mutations A30P and A53T. Neurotoxicology 23(4-5):553-567.
Abstract: Structural properties and response to changes in the environment of wild-type (WT), A30P and A53T alpha-synucleins, as well

as their propensity to aggregate or form fibrils, were compared by a variety of biophysical methods, including far-UV CD, FTIR, SAXS, static light scattering and Thioflavin T (TFT) fluorescence. All three proteins were natively unfolded under physiological conditions but adopted identical partially-folded conformations under conditions of acidic pH or high temperature. The initial kinetic event in the fibrillation of all three alpha-synucleins was shown to be the formation of a partially-folded intermediate with properties close to those described for these proteins at acidic pH or at high temperatures. Both mutants showed a greater propensity to form non-fibrillar aggregates than wild-type protein. All three proteins formed fibrils faster in the presence of heparin, although substantially higher concentrations were required for the A30P mutant. In contrast to the wild-type and A53T proteins, in which fibrillation was further accelerated by the presence of the pesticide diethyldithiocarbamate (DDC), the A30P mutant was inhibited by DDC. The mutant proteins had significantly lower affinity for DDC than the WT. A model of the effect of mutations on the aggregation behavior of alpha-synuclein is proposed, which explains the different effects of exogenous agents on the three proteins, based on different kinetic partitioning along pathways leading to fibrils and to non-fibrillar aggregates. 

Li SG, Crooks PA, Wei SC, De Leon J. 2004. Toxicity of dipyridyl compounds and related compounds. Crit Rev Toxicol 34(5):447-460.
Abstract: Five dipyridyl isomers, 2,2'-, 2,3-, 2,4'-, 3,3'-, and 4,4'-dipyridyl, are products resulting from the pyrolytic degradation of tobacco products and degradation of the herbicide paraquat, and therefore may be present in the environment. In this article, the toxicological properties of these dipyridyl isomers in humans and animals are reviewed. Epidemiological studies suggest that cancerous skin lesions in workers involved in the manufacturing of paraquat may be associated with exposure to dipyridyl compounds. Experimental animal studies suggest that dipyridyl isomers may have several toxicological effects. Three of the dipyridyl isomers (the 2,2', 2,4', and 4,4' isomers) appear to be inducers of some metabolic enzymes. The 2,2'-dipyridyl isomer, an iron chelator, appears to influence vasospasm in primate models of stroke. The cytotoxic effects of 2,2-dipyridyl on several leukemia cell lines have been reported, and a potent teratogenic effect of 2,2'-dipyridyl has been observed in rats. Based on the results of paraquat studies in experimental animal models, it has been proposed that paraquat may have deleterious effects on dopaminergic neurons. These findings support the epidemiological evidence that paraquat exposure may be associated with the development of Parkinson's disease. Studies designed to determine an association between paraquat exposure and Parkinson's disease are complicated by the possibility that metabolic changes may influence the neurotoxicity of paraquat and/or its metabolites. Preliminary unpublished data in mice show that 300-mg/kg doses of 2,2'-dipyridyl are neurotoxic, and 300-mg/kg doses of 2,4'- and 4,4'-dipyridyls are lethal. These results are consistent with earlier studies in Sherman rats using high 2,2'- and 4,4'-dipyridyl doses. New studies are needed to further explore the toxicological properties of dipyridyls and

their potential public health impact.

Li X, Matsumoto K, Murakami Y, Tezuka Y, Wu YL, Kadota S. 2005. Neuroprotective effects of Polygonum multiflorum on nigrostriatal dopaminergic degeneration induced by paraquat and maneb in mice. Pharmacol Biochem Behav 82(2):345-352.
Abstract: The neuroprotective effects of Polygonum multiflorum extract (PME) and its two fractions, ethanol-soluble PME (PME-I) and -insoluble PME (PME-II), on the degeneration of nigrostriatal dopaminergic neurons induced by a combination of paraquat and maneb (PQMB) were investigated in male C57BL/6 mice. The mice were treated twice a week for 6 weeks with intraperitoneal injections of PQMB. This combination caused a reduction of spontaneous locomotor activity, motor incoordination, and declines of dopamine level in the striatum and tyrosine hydroxylase-positive neurons in the substantia nigra. Administration of PME and PME-I once daily for 47 days during 6 weeks of PQMB treatment and last 8 days after PQMB significantly attenuated the impairment of behavioral performance and the decrease in striatal dopamine level and substantia nigral tyrosine hydroxylase-positive neurons in the PQMB-treated animals, whereas the administration of PME-II had no effect on these behavioral, neurochemical and histological indices. The present findings suggest that PME has a beneficial influence on parkinsonism induced by PQMB and that the effects of PME are attributable to some substance(s) included in the ethanol-soluble fraction of PME (PME-I). (C) 2005 Elsevier Inc. All rights reserved.

Li X, Sun AY. 1999. Paraquat induced activation of transcription factor AP-1 and apoptosis in PC12 cells. J Neural Transm 106(1):1-21 .
Abstract: Drugs and certain environmental toxins may be responsible for the pathogenesis of Parkinson's disease. We have used paraquat as a model toxin for this study since paraquat has been shown to make its way to the nerve terminals and cause cell death of dopamine neurons by oxidative injury. We have shown by the electrophoretic mobility shift assay that paraquat, together with low concentrations of chelated iron (Fe++/ DETAPAC), induced the activation of transcription factor AP-1 binding activity to DNA. Under similar conditions we also found by both a DNA laddering assay procedure and by terminal deoxynucleotidyl transferase assay (TUNEL assay) that paraquat also induces apoptotic cell death. Interestingly, both apoptotic cell death and AP-1/DNA binding activity induced by paraquat were blocked by cyclohexamide and genistein, indicating that both the AP-1/DNA binding activation and apoptosis induced by paraquat are closely related. Moreover, cells were also protected from paraquat toxicity in the presence of antioxidant defense enzymes SOD and catalase. The results support the hypothesis that oxidative stress may be contributing to the apoptotic cell death of-dopaminergic neurons, leading to the manifestation of Parkinson's disease. Since paraquat was an important herbicide in the mid 20th Century, our results have the important implication that exposure to environmental toxins such as paraquat may induce Parkinson's disease.

Li X, Yin J, Cheng CM, Sun JL, Li Z, Wu YL. 2005. Paraquat induces selective dopaminergic nigrostriatal degeneration in aging C57BL/6 mice. Chin Med J (Engl) 118(16):1357-1361.
Abstract: Background Paraquat (PQ; 1,1'-dimethyl-4,4'-bipyridinium), a widely used herbicide that is structurally similar to the known dopaminergic neurotoxicant MPTP (1-methyl-1, 2, 3, 6-tetrahydropyridine), has been suggested as a potential etiologic factor for the development of Parkinson's disease (PD). Aging is an accepted risk factor for idiopathic Parkinson's disease. The aim of this study was to test the hypothesis that paraquat could induce PD-like nigrostriatal dopaminergic degeneration in aging C57BL/6 mice. Methods Senile male C57BL/6 mice were intraperitoneally injected with either saline or PQ at 2-day intervals for a total of 10 doses. Locomotor activity and performance on the pole test were measured 7 days after the last injection and animals were sacrificed one day later. Level of dopamine (DA) and its metabolites levels in the striatum were measured by high-performance liquid chromatography with an electrochemical detector (HPLCECD), and numbers of tyrosine hydroxylase (TH) positive neurons were estimated using inummohistochemistry. Results Locomotor activities were significantly decreased and the behavioral performance on the pole test were significantly impaired in the PQ treated group. Level of DA and its metabolites levels in the striatum were declined by 8 days after the last injection. Immunohistochemical analyses showed that PQ was associated with a reduction in numbers of tyrosine hydroxylase positive neurons. Conclusions Long-term repeated exposes to PQ can selectively impair the nigrostriatal dopaminergic system of senile mice, suggesting that PQ could play an important role in the pathogenesis of Parkinson's disease ( PI) Our results also validate a novel model of PD) induced by exposure to a toxic environmental agent.

Lindquist NG, Larsson BS, Lyden-Sokolowski A . 1988 Oct 31. Autoradiography of 14C paraquat or [14C]diquat in frogs and mice: accumulation in neuromelanin. Neurosci Lett 93(1):1-6.
Abstract: The herbicide paraquat has been suggested as a causative agent for Parkinson's disease because of its structural similarity to a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which may induce a parkinsonism-like condition. MPTP as well as its metabolite 1-methyl-4-phenylpyridine have melanin affinity, and the parkinsonism-inducing potency of MPTP is much stronger in species with melanin in the nerve cells. Autoradiography of [3H]MPTP in experimental animals has shown accumulation in melanin-containing tissues, including pigmented neurons. In the present whole body autoradiographic study accumulation and retention was seen in neuromelanin in frogs after i.p. injection of [14C] paraquat or [14C]diquat. By means of whole body autoradiography of [14C]diquat in mice (a species with no or very limited amounts of neuromelanin) a low, relatively uniformly distributed level of radioactivity was observed in brain tissue. Accumulation of toxic chemical compounds, such as paraquat, in neuromelanin may ultimately cause lesions in the pigmented nerve cells, leading to Parkinson's disease.

Ling ZD, Chang QA, Tong CW, Leurgans SE, Lipton JW, Carvey PM. 2004.

Rotenone potentiates dopamine neuron loss in animals exposed to lipopolysaccharide prenatally. Exp Neurol 190(2):373-383.
Abstract: We previously demonstrated that treating gravid female rats with the bacteriotoxin lipopolysaccharide (LPS) led to the birth of offspring with fewer than normal dopamine (DA) neurons. This DA neuron loss was long-lived and associated with permanent increases in the proinflammatory cytokine tumor necrosis factor alpha (TNFalpha). Because of this pro-inflammatory state, we hypothesized that these animals would be more susceptible to subsequent exposure of DA neurotoxins. We tested this hypothesis by treating female Sprague Dawley rats exposed to LPS or saline prenatally with a subtoxic dose of the DA neurotoxin rotenone (1.25 mg/kg per day) or vehicle for 14 days when they were 16 months old. After another 14 days, the animals were sacrificed. Tyrosine hydroxylase-immunoreactive (THir) cell counts were used as an index of DA neuron survival. Animals exposed to LPS prenatally or rotenone postnatally exhibited a 22% and 3%, respectively, decrease in THir cell counts relative to controls. The combined effects of prenatal LPS and postnatal rotenone exposure produced a synergistic 39% THir cell loss relative to controls. This loss was associated with decreased striatal DA and increased striatal DA activity ([HVA]/[DA]) and TNFalpha. Animals exposed to LPS prenatally exhibited a marked increase in the number of reactive microglia that was further increased by rotenone exposure. Prenatal LPS exposure also led to increased levels of oxidized proteins and the formation of alpha-Synuclein and eosin positive inclusions resembling Lewy bodies. These results suggest that exposure to low doses of an environmental neurotoxin like rotenone can produce synergistic DA neuron losses in animals with a preexisting pro-inflammatory state. This supports the notion that Parkinson's disease (PD) may be caused by multiple factors and the result of "multiple hits" from environmental toxins. (C) 2004 Elsevier Inc. All rights reserved.

Liou HH, Chen RC, Chen THH, Tsai YF, Tsai MC . 2001. Attenuation of paraquat-induced dopaminergic toxicity on the substantia nigra by (-)-deprenyl in vivo. Toxicol Appl Pharmacol 172(1):37-43.
Abstract: (-)-Deprenyl (DEP) had been shown to slow of progression of Parkinson's disease (PD). The present study sought to determine whether DEP would attenuate the nigrostriatal system damage induced by intranigral administration of the herbicide paraquat (PQ) as a model of parkinsonism in vivo. Neurochemical and behavioral observations of Wistar rats were the focus of our study. In the neurochemical observation, the PQ injected in the rats caused dose-dependent depletion of dopamine (DA) in the ipsilateral striata. The coadministration of DEP with PQ partially increased the striatal DA level. The prediction of the striatal DA levels was calculated by regression coefficients obtained from multiple linear regression ($r(2) = 0.82$): DA level (% of control) = 103.34 - 9.58 PQ (nmol) + 0.79 DEP (nmol). It was demonstrated that the high dose of 20 nmol DEP could significant attenuate the PQ (5 nmol)-elicited dopaminergic toxicity ($p < 0.05$). In the behavioral observation, the intranigral injection of PQ into the rats caused a rotation behavior contralateral to the lesioned

side in response to apomorphine administration (0.5 mg/kg, sc). This apomorphine-induced rotational behavior could also be attenuated significantly by coadministration of DEP (20 nmol) and PQ (5 nmol) compared with PQ-treated (5 nmol) animals ($p < 0.05$). The above observations indicate that DEP could provide a protective effect on the moderate injury elicited by PQ toxicity of the nigro-strital dopaminergic system. DEP might be a useful therapeutic agent in treating patients with early-stage PD. (C) 2001 Academic Press.

Liou HH, Chen RC, Tsai YF, Chen WP, Chang YC, Tsai MC. 1996. Effects of paraquat on the substantia nigra of the Wistar rats: Neurochemical, histological, and behavioral studies. Toxicol Appl Pharmacol 137(1):34-41.
Abstract: Effects of paraquat on the substantia nigra of the male Wistar rats were studied pharmacologically by a intracerebral injection of paraquat. The neurochemical, morphological, and behavioral changes observed after a unilateral intranigral injection of paraquat (1-5 mu g) were as follows: (1) neurochemically, paraquat caused dose-dependent depletion of dopamine in the ipsilateral striatum starting 2 weeks after treatment; this effect was longlasting and irreversible. The ipsilateral striatal dopamine level in animals treated with 3 mu g paraquat was even decreased by 91.5%. (2) Morphologically, 2 mu g of paraquat produced marked loss of Nissl substances and prominent glial reaction in the substantia nigra, while 3 mu g of paraquat caused a severe loss of neurons. (3) Behaviorally, paraquat caused a vigorous rotational behavior in rats contralateral to the lesioned side in response to apomorphine administration (0.5 mg/kg, sc). This effect was dose-dependent and lasted for the entire 16-week experimental period. Taken together, these data indicate that intranigrally injected paraquat may possess marked neurotoxicity and induce degeneration of the rat nigrostriatal dopaminergic system. (C) 1996 Academic Press, Inc.

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC. 1997. Environmental risk factors and Parkinson's disease: A case-control study in Taiwan. Neurology 48(6):1583-1588.
Abstract: To explore environmental risk factors for Parkinson's disease (PD) in Taiwan, we investigated 120 patients with PD and 240 hospital control subjects matched with patients on age (+/-2 years) and sex. Based on a structured open-ended questionnaire, we carried out standardized interviews to obtain history of exposure to environmental factors, including place of residence, source of drinking water, and environmental and occupational exposures to various agricultural chemicals. In the univariate analysis, the history of living in a rural environment, farming, use of herbicides/pesticides, and use of paraquat were associated with an increased PD risk in a dose-response relationship. After adjustment for multiple risk factors through conditional logistic regression, the biological gradient between PD and previous uses of herbicides/pesticides and paraquat remained significant. The PD risk was greater among subjects who had used paraquat and other herbicides/pesticides than those who had used herbicides/pesticides other than paraquat. There were no significant differences in occupational exposures to chemicals, heavy metals, and

minerals between PD patients and matched control subjects. The duration of drinking well water and alcohol consumption was not significantly associated with PD. There was an inverse relationship between cigarette smoking and PD. Environmental factors, especially exposures to paraquat and herbicides/pesticides, may play important roles in the development of PD in Taiwan.

Liu B, Gao HM, Hong JS. 2003. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: Role of neuroinflammation. Environ Health Perspect 111(8):1065-1073.
Abstract: Idiopathic Parkinson's disease (PD) is a devastating movement disorder characterized by selective degeneration of the nigrostriatal dopaminergic pathway. Neurodegeneration usually starts in the fifth decade of life and progresses over 5-10 years before reaching the fully symptomatic disease state. Despite decades of intense research, the etiology of sporadic PD and the mechanism underlying the selective neuronal loss remain unknown. However, the late onset and slow-progressing nature of the disease has prompted the consideration of environmental exposure to agrochemicals, including pesticides, as a risk factor. Moreover, increasing evidence suggests that early-life occurrence of inflammation in the brain, as a consequence of either brain injury or exposure to infectious agents may play, a role in the pathogenesis of PD. Most important, there may be a self-propelling cycle of inflammatory process involving brain immune cells (microglia and astrocytes) that drives the slow yet progressive neurodegenerative process. Deciphering the molecular and cellular mechanisms governing those intricate interactions would significantly advance our understanding of the etiology and pathogenesis of PD and aid the development of therapeutic strategies for the treatment of the disease.

Liu HQ, Zhu XZ, Weng EQ. 2005. Intracellular dopamine oxidation mediates rotenone-induced apoptosis in PC12 cells. Acta Pharmacologica Sinica 26 (1):17-26.
Abstract: Aim: To study the role of dopamine (DA) in rotenone-induced neurotoxicity in PC 12 cells. Methods: Cell viability was assessed by detecting the leakage of lactate dehydrogenase (LDH) into the medium. Apoptosis rate was measured by flow cytometry. Caspase-3-like activity was measured by fluorescence assay using the probe Ac-DEVD-AMC. The level of intracellular hydrogen peroxide and other peroxides in PC12 cells were quantified by loading cells with 2'-7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) in fluorescence assay. Lactic acid was measured spectrophotometrically. The DA levels in PC12 cells were determined by HPLC-ECD. Results: A 48-h incubation of PC12 cells with rotenone caused an apoptotic cell death and elevated intracellular reactive oxygen species (ROS) and lactic acid accumulation. Intracellular DA depletion with reserpine significantly attenuated rotenone-induced ROS accumulation and apoptotic cell death. No change was found in rotenone-induced ROS accumulation when cells were co-treated with deprenyl. Brief treatment with reserpine at the end of rotenone treatment had no effect on rotenone-induced neurotoxicity. However, when cells were first incubated with

deprenyl, a monoamine oxidase-B inhibitor for 30 min then co-incubated with rotenone plus deprenyl, a brief treatment with reserpine enhanced cell injury. Conclusion: Rotenone-induced apoptosis in PC12 cells was mediated by intracellular dopamine oxidation.

Liu WF. 1996. Effects of antimuscarinic antiparkinsonian drugs on brightness discrimination performance in rats. Pharmacol Biochem Behav 54(2): 425-430.
Abstract: Biperiden (BPR) and trihexyphenidyl (THP), the current antimuscarinic drugs of choice in the management of parkinsonism, have been shown to exert anticonvulsant effects induced by poisoning by the organophosphorus compound soman. The present study was undertaken to evaluate the effects of these drugs on performance of a simple light-intensity discrimination task in rats under a tandem schedule of fixed-ratio (FR) reward/ differential-reinforcement-of-low-rate (DRL) nonreward contingencies, for water reinforcement in 2-h experimental sessions. Both BPR (0.125-2.0 mg/kg, SC) and THP (0.25-8.0 mg/kg, SC) in general decreased overall reinforcement rates in a similar dose dependent and parallel manner, concurrent with increased overall nonreinforced responses in an inverted U-shaped dose-response relationship. Lower doses of BPR (0.125-0.5 mg/kg) and and THP (0.25-2.0 mg/kg) produced a moderate reduction in reinforcement (greater than or equal to 50% of baseline controls), which was correlated well with increases in nonreinforced responses emitted, whereas, higher doses of BPR (>0.5 mg/kg) and TPH (greater than or equal to 2.0 mg/kg) markedly decreased reinforcements, which mainly resulted from the pausing of responding in the presence of stereotyped behavior. The behavioral disruption induced by BPR was much more rapid than that induced by THP. The ED(50) values (0.6 mg/kg vs. 1.3 mg/kg, respectively) and parallel dose-effect curves suggest that these drugs have similar efficacy, and that BPR is about twice as potent as THP, a ranking that corresponds with their binding affinity at M-1 muscarinic acetylcholine receptors in rat cerebral cortex. Based on the similarity between the anticonvulsant doses of these drugs and the maximal doses that in this study did not disrupt operant responses (0.125 mg/kg vs. 0.25 mg/kg, respectively), it is suggested that both drugs may be useful in protection against seizures produced by the cholinesterase inhibitor soman. Overall, these results suggest that this multiple schedule operant contingency may have promise as a behavioral model to identify the therapeutic or toxic potentials of centrally acting antimuscarinic antiparkinsonian drugs based on their congnitive side effects.

Liu X, Wu JY, Zhou F, Sun XL, Yao HH, Yang Y, Ding JH, Hu G. 2006 Feb 13. The regulation of rotenone-induced inflammatory factor production by ATP-sensitive potassium channel expressed in BV-2 cells. Neurosci Lett 394(2): 131-5.
Abstract: Our previous studies have demonstrated that activating ATP-sensitive potassium channel (K(ATP) channel), not only improved Parkinsonian behavior and neurochemical symptoms, but also reduced iNOS activity and mRNA levels in striatum and nigra of rotenone rat model of Parkinson's disease (PD). In this study, it was first shown that the

subunits of K(ATP) channels are expressed in BV-2 cells, and then it was investigated whether K(ATP) channel was involved in regulating inflammatory factor production from BV-2 cells activated by rotenone. It was found that K(ATP) channel was expressed in BV-2 cell and formed by the combination of Kir 6.1 and SUR 2A/2B. K(ATP) channel openers (KCOs) including pinacidil, diazoxide and iptakalim (Ipt) exerted beneficial effects on rotenone-induced morphological alterations of BV-2 cells, decreased tumor necrosis factor alpha (TNF-alpha) production and the expression and activity of inducible isoform of nitric oxide synthase (iNOS). Either glibenclamide or 5-hydroxydecanoate acid (a selective mitochondrial K (ATP) channel blocker) could abolish the effects of KCOs, suggesting that K (ATP) channels, especially mitochondrial ATP-sensitive potassium channels (mitoK(ATP) channels), played a crucial role in preventing the activation of BV-2 cells, and subsequently the production of a variety of proinflammatory factors. Therefore, activation of K(ATP) channel might be a new therapeutic strategy for treating neuroinflammatory and neurodegenerative disorders.

Lockridge O, Masson P. 2000. Pesticides and susceptible populations: People with butyrylcholinesterase genetic variants may be at risk. Neurotoxicology 21 (1-2):113-126.
Abstract: Butyrylcholinesterase (BChE) scavenges low doses of organophosphorus (for example, paraoxon) and carbamate pesticides (for example, carbaryl) and in this way protects people from the toxic effects of these poisons. The protective role of BChE is demonstrated by the finding that pesticide applicators can have reduced BChE activity with no clinical signs of poisoning. The question has arisen whether people with genetic variants of BChE are less protected. Seventy-six percent of the population is homozygous for wildtype BChE, while 24% carry at least one genetic variant allele. Most genetic variants of BChE have reduced activity. The clinically most important variant is atypical (D70G) BChE because people with this variant have 2 hours of apnea after receiving a dose of succinylcholine that is intended to paralyze muscles for 3-5 minutes. In test tube experiments the atypical variant reacts more slowly with all positively charged compounds (for example physostigmine, echothiophate). This leaves more toxin available for reaction with acetyl cholinesterase in nerve synapses and predicts that people with atypical BChE will be less protected. Variants with low activity, such as silent BChE, are predicted to be at increased risk from organophosphorus pesticides based on experiments in monkeys and rodents where injection of purified BChE protected animals from the toxic effects of nerve agents. More studies are needed to strengthen the hypothesis that people with genetic variants of BChE are at higher risk of intoxication from pesticides. (C) 2000 Inter Press, Inc.

Lockwood AH. 2000. Pesticides and Parkinsonism: is there an etiological link? Curr Opin Neurol 13(6):687-690.
Abstract: Two hundred years ago, Parkinson's disease was rare. Now, it is the second most common neurodegenerative disorder. A recent twin study showed clearly that genetic factors play a minor role in determining whether an individual develops this disease, rekindling an interest in the

etiological significance of environmental factors. Earlier studies had shown that a MPTP, a contaminant found in some illegal drugs. caused Parkinson's disease. This provided the original impetus for the pesticide hypothesis. Similarities between MPTP and pesticides coupled with epidemiological and animal studies have strengthened the possible link between pesticide exposure and the subsequent development of Parkinson's disease. Curr Opin Neurol 13:687-690 (C) 2000 Lippincott Williams & Wilkins.

Lockwood AH. 2002. Organophosphate pesticides and public policy. Curr Opin Neurol 15(6):725-729.

Lockwood AH. 2004. Human testing of pesticides: Ethical and scientific considerations. Am J Public Health 94(11):1908-1916.

Logroscino G. 2005. The role of early life environmental risk factors in Parkinson disease: what is the evidence? Environ Health Perspect 113(9):1234-1238. Abstract: Parkinson disease (PD) is of unknown but presumably multifactorial etiology. Neuropathologic studies and animal models show that exposure to environmental neurotoxicants can determine progressive damage in the substantia nigra many years before the onset of clinical parkinsonism. Therefore, PD, like other neurologic diseases related to aging, may be determined by exposures present in the environment early during the life span or even during pregnancy. Recent epidemiologic studies have focused on the possible role of environmental risk factors present during adult life or aging. Smoking and coffee drinking have consistently been identified to have protective associations, whereas roles of other risk factors such as pesticide and infections have been reported in some studies but not replicated in others. Both genetic inheritance and sharing of common environment in the same family explain the increased risk of PD of relatives of PD cases compared with relatives of controls in familial aggregation studies. Much evidence indicates that risk factors that have a long latency or a slow effect could be important for late-onset PD. Further epidemiologic studies are warranted in this area.

Lotharius J, O'malley KL. 2000. The Parkinsonism-inducing drug 1-methyl-4-phenylpyridinium triggers intracellular dopamine oxidation - A novel mechanism of toxicity. J Biol Chem 275(49):38581-38588. Abstract: Uptake of the Parkinsonism-inducing toxin, 1-methyl-4-phenylpyridinium (MPP+), into dopaminergic terminals is thought to block Complex I activity leading to ATP loss and overproduction of reactive oxygen species (ROS). The present study indicates that MPP+-induced ROS formation is not mitochondrial in origin but results from intracellular dopamine (DA) oxidation. Although a mean lethal dose of MPP+ led to ROS production in identified dopaminergic neurons, toxic doses of the Complex I inhibitor rotenone did not. Concurrent with ROS formation, MPP+ redistributed vesicular DA to the cytoplasm prior to its extrusion from the cell by reverse transport via the DA transporter. MPP+-induced DA redistribution was also associated with cell death. Depleting cells of newly synthesized and/or stored DA significantly attenuated both superorxide production and cell death, whereas enhancing intracellular DA content

exacerbated dopaminergic sensitivity to MPP+. Lastly, depleting cells of DA in the presence of succinate completely abolished MPP+-induced cell death. Thus, MPP+ neurotoxicity is a multi-component process involving both mitochondrial dysfunction and ROS generated by vesicular DA displacement. These results suggest that in the presence of a Complex I defect, misregulation of DA storage could lead to the loss of nigrostriatal neurons in Parkinson's disease.

Lotharius J, O'malley KL. 2001. Role of mitochondrial dysfunction and dopamine-dependent oxidative stress in amphetamine-induced toxicity. Ann Neurol 49(1):79-89.
Abstract: To define the molecular mechanisms underlying amphetamine (AMPH) neurotoxicity, primary cultures of dopaminergic neurons were examined for drug-induced changes in dopamine (DA) distribution, oxidative stress, protein damage, and cell death. As in earlier studies, AMPH rapidly redistributed vesicular DA to the cytoplasm, where it underwent out cp-ard transport through the DA transporter. DA was concurrently oxidized to produce a threefold increase in free radicals, as measured by the redox-sensitive dye dihydroethidium. Intracellular DA depletion using the DA synthesis inhibitor alpha -methyi-p-tyrosine or the vesicular monoamine transport blocker reserpine prevented drug-induced free radical formation. Despite these AMPH-induced changes, neither protein oxidation nor cell death was observed until 1 and 4 days, respectively. AMPH also induced an early burst of free radicals in a CNS-derived dopaminergic cell line. However, AMPH-mediated attenuation of ATP production and mitochondrial function was not observed in these cells until 48 to 72 hours. Thus, neither metabolic dysfunction nor loss of viability was a direct consequence of AMPH neurotoxicity. In contrast, when primary cultures of dopaminergic neurons were exposed to AMPH in the presence of subtoxic doses of the mitochondrial complex I inhibitor rotenone, cell death was dramatically increased, mimicking the effects of a known parkinsonism-inducing toxin. Thus, metabolic stress may predispose dopaminergic neurons to injury by free radical-promoting insults such as AMPH.

Maggio R, Riva M, Vaglini F, Fornai F, Molteni R, Armogida M, Racagni G, Corsini GU. 1998. Nicotine prevents experimental parkinsonism in rodents and induces striatal increase of neurotrophic factors. J Neurochem 71(6): 2439-2446.
Abstract: The repeated finding of an apparent protective effect of cigarette smoking on the risk of Parkinson's disease is one of the few consistent results in the epidemiology of this disorder. Among the numerous substances that originate from tobacco smoke, nicotine is by far the most widely studied. Nicotine is a natural alkaloid that has considerable stimulatory effects on the CNS. Its effects on the CNS are mediated by the activation of neuronal heteromeric acetylcholine-gated ion channel receptors (nAChRs, also termed nicotinic acetylcholine receptors), In the present study, we describe the neuroprotective effects of (-)-nicotine in two animal models of parkinsonism: diethyldithiocarbamate-induced enhancement of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in

mice and methamphetamine-induced neurotoxicity in rats and mice. The neuroprotective effect of (-)-nicotine was very similar to that of the noncompetitive NMDA receptor antagonist (+)-MK-801, In parallel experiments, we found that (-)-nicotine induces the basic fibroblast growth factor-2 (FGF;2) and the brain-derived neurotrophic factor in rat striatum, The effect of(-)nicotine on the induction of FGF-2 was prevented by the nAChR antagonist mecamylamine. We also found that (+)-MK-801 was able to induce FGF-2 in the striatum. As trophic factors have been reported to be neuroprotective for dopaminergic cells, our data suggest that the increase in neurotrophic factors is a possible mechanism by which (-)-nicotine protects from experimental parkinsonisms.

Maggio R, Riva M, Vaglini F, Fornai F, Racagni G, Corsini GU. 1997. Striatal increase of neurotrophic factors as a mechanism of nicotine protection in experimental parkinsonism. J Neural Transm 104(10):1113-1123. Abstract: The repeated finding of an apparent protective effect of cigarette smoking on the risk of Parkinson's disease is one of the few consistent results in the epidemiology of this disorder. Among the innumerous substances that originate from tobacco smoke, nicotine is by far the most widely studied, and the most likely candidate for a protective effect against neuronal degeneration in Parkinson's disease. Nicotine is a natural alkaloid that has considerable stimulatory effects on the central nervous system (CNS). Its effects on the CNS are mediated by the activation of neuronal heteromeric acetylcholine-gated ion channel receptors (nAChR, also termed nicotinic acetylcholine receptors). In the present study, we describe the neuroprotective effects of (-)nicotine in two animal models of parkinsonism: the diethyldithiocarbamate (DDC)-induced enhancement of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in mice, and the methamphetamine-induced neurotoxicity in rats and mice. In parallel experiments, we found that (-)nicotine induces the basic fibroblast growth factor (FGF-2) and the brain-derived neurotrophic factor (BDNF) in rat striatum. As FGF-2 and BDNF have been reported to be neuroprotective for dopaminergic cells, our data indicate that the increase in neurotrophic factors is a possible mechanism by which (-)nicotine protects from experimental parkinsonisms. Moreover, they suggest that nAChR agonists could be of potential benefit in the progression of Parkinson's disease.

Maher NE, Golbe LI, Lazzarini AM, Mark MH, Currie LJ, Wooten GF, Saint-Hilaire M, Wilk JB, Volcjak J, Maher JE, Feldman RG, Guttman M, Lew M, Schuman S, Suchowersky O, Lafontaine AL, Labelle N, Vieregge P, Pramstaller PP, Klein C, Hubble J, Reider C, Growdon J, Watts R, Montgomery E, Baker K, Singer C, Stacy M, Myers RH. 2002. Epidemiologic study of 203 sibling pairs with Parkinson's disease - The GenePD study. Neurology 58(1):79-84. Abstract: Objective: To examine patterns of familial aggregation and factors influencing onset age in a sample of siblings with PD. Methods: Sibling pairs (n = 203) with PD were collected as part of the GenePD study. Standardized family history, medical history, and risk factor data were collected and analyzed. Results: The mean age at onset was 61.4 years and did not differ according to sex, exposure to coffee, alcohol, or pesticides. Head trauma was associated with younger onset (P = 0.03) and

multivitamin use with later onset (p = 0.007). Age at onset correlation between sibling pairs was significant (r = 0.56, P = 0.001) and was larger than the correlation in year of onset (r = 0.29). The mean difference in onset age between siblings was 8.7 years (range, 0 to 30 years). Female sex was associated with increased frequency of relatives with PD. The frequency of affected parents (7.0%) and siblings (5.1%) was increased when compared with frequency in spouses (2.0%). Conclusions: The greater similarity for age at onset than for year of onset in sibling pairs with PD, together with increased risk for biological relatives over spouses of cases, supports a genetic component for PD. Risk to siblings in this series is increased over that seen in random series of PD cases; however, patients in this sample have similar ages at onset and sex distribution as seen for PD generally. These analyses suggest that factors influencing penetrance are critical to the understanding of this disease.

Mailman RB. 1987 Nov-Dec. Mechanisms of CNS injury in behavioral dysfunction. Neurotoxicol Teratol 9(6):417-26.

Abstract: Advances in the neurosciences have led to a greater understanding of the anatomical, biochemical, and molecular loci involved in injury to, and adaptation of, the central nervous system. Recent research has permitted the elucidation of the mechanisms for some neurotoxicants whose actions have been studied for decades, as in the example of the pyrethroid insecticides. In contrast, the mechanism of the neurotoxicity of the organophosphate insecticides and nerve gases has been known for many years, but our understanding of the many resulting sequelae has been markedly increased by recent discoveries. Two examples illustrate the strengths and weaknesses of such methods in predicting neurotoxicity. Studies of the parkinsonian-like toxicity caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (a by-product of synthesis of illicit opiates) exemplify the best application of current methods in neurotoxicology. It has been shown that the expression of MPTP toxicity requires both metabolism of MPTP to the proximal toxicant 1-methyl-4-phenylpyridinium (MPP+) and active uptake into central dopamine neurons. The discovery of binding sites of MPP+ in these cells has clarified how dopamine neurons are destroyed, thereby causing neurological signs. This illustrates two key concepts: first, the bioconversion of compounds to proximal toxicants is often ignored, and second, these events are unlikely to be detectable by in vitro studies that focus on a few biochemical endpoints. Another useful example was that of erythrosin (FD&C Red No. 3), in which numerous in vitro studies suggested that this food color was a potential neurotoxicant. However, this was shown to be an artifact of the ability of this color to disrupt biomembranes at high in vitro concentrations, and this idea was supported by negative data from both behavioral and clinical studies. Thus, the plethora of possible molecular and biochemical targets in the central nervous system (receptors, second messenger events, transmitter-modulator synthesis, storage and release, membrane maintenance, etc.) preclude the likelihood of developing a single test or a battery of neurochemical or biochemical tests that will be able to screen for neurotoxicants randomly or efficiently.

Use of in vitro methods is likely to detect both false positives and negatives. While the availability of theoretical or phenomenological data provides the best start to the application of available biochemical and molecular techniques, predictions of neurotoxicity best can come from theoretical comparison of the structure of suspect compounds (and hypothesized metabolites) with known target sites in the CNS.(ABSTRACT TRUNCATED AT 400 WORDS)

Manning-Bog AB, Mccormack AL, Li J, Uversky VN, Fink AL, Di Monte DA. 2002. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice - Paraquat and alpha-synuclein. J Biol Chem 277(3): 1641-1644.
Abstract: alpha-Synuclein-containing aggregates represent a feature of a variety of neurodegenerative disorders, including Parkinson's disease (PD). However, mechanisms that promote intraneuronal alpha-synuclein assembly remain poorly understood. Because pesticides, particularly the herbicide paraquat, have been suggested to play a role as PD risk factors, the hypothesis that interactions between alpha-synuclein and these environmental agents may contribute to aggregate formation was tested in this study. Paraquat markedly accelerated the in vitro rate of alpha-synuclein fibril formation in a dose-dependent fashion. When mice were exposed to the herbicide, brain levels of alpha-synuclein were significantly increased. This up-regulation followed a consistent pattern, with higher alpha-synuclein at 2 days after each of three weekly paraquat injections and with protein levels returning to control values by day 7 post-treatment. Paraquat exposure was also accompanied by aggregate formation. Thioflavine S-positive structures accumulated within neurons of the substantia nigra pars compacta, and dual labeling and confocal imaging confirmed that these aggregates contained alpha-synuclein. The results suggest that up-regulation of alpha-synuclein as a consequence of toxicant insult and direct interactions between the protein and environmental agents are potential mechanisms leading to alpha-synuclein pathology in neurodegenerative disorders.

Manning-Bog AB, Mccormack AL, Purisai MG, Bolin LM, Di Monte DA. 2003. alpha-synuclein overexpression protects against paraquat-induced neurodegeneration. J Neurosci 23(8):3095-3099.
Abstract: alpha-Synuclein is likely to play a role in neurodegenerative processes, including the degeneration of nigrostriatal dopaminergic neurons that underlies Parkinson's disease. However, the toxicological properties of alpha-synuclein remain relatively unknown. Here, the relationship between alpha-synuclein expression and neuronal injury was studied in mice exposed to the herbicide paraquat. Paraquat neurotoxicity was compared in control animals versus mice with transgenic expression of human alpha-synuclein driven by the tyrosine hydroxylase (TH) promoter. In control mice, paraquat caused both the formation of alpha-synuclein-containing intraneuronal deposits and the degeneration of nigrostriatal neurons, as demonstrated by silver staining and a reduction of the counts of TH-positive and Nissl-stained cells. Mice overexpressing alpha-synuclein, either the human wild-type or the Ala53Thr mutant form of the protein,

displayed paraquat-induced protein aggregates but were completely protected against neurodegeneration. These resistant animals were also characterized by increased levels of HSP70, a chaperone protein that has been shown to counteract paraquat toxicity in other experimental models and could therefore contribute to neuroprotection in alpha-synuclein transgenic mice. The results indicate a dissociation between toxicant-induced alpha-synuclein deposition and neurodegeneration. They support a role of alpha-synuclein against toxic insults and suggest that its involvement in human neurodegenerative processes may arise not only from a gain of toxic function, as previously proposed, but also from a loss of defensive properties.

Mao WK, Qin FZ, Iwai CK, Vulapalli RJ, Keng PC, Liang CS. 2004. Extracellular norepinephrine reduces neuronal uptake of norepinephrine by oxidative stress in PC12 cells. American Journal of Physiology-Heart and Circulatory Physiology 287(1):H29-H39.
Abstract: Cardiac norepinephrine ( NE) uptake activity is reduced in congestive heart failure. Our studies in intact animals suggest that this effect on the cardiac sympathetic nerve endings is caused by oxidative stress and/or NE toxic metabolites derived from NE. In this study, we investigated the direct effects of NE on neuronal NE uptake activity and NE transporter (NET), using undifferentiated PC12 cells. Cells were incubated with NE (1-500 muM) either alone or in combination of Cu2+ sulfate (1 muM), which promotes free radical formation by Fenton reaction for 24 h. NE uptake activity was measured using [H-3]NE. Cell viability was determined with the use of Trypan blue exclusion and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide assay, and cellular oxidative stress by dichlorodihydrofluorescein fluorescence and the GSH/GSSG ratio. Cell viability was reduced by NE > 100 muM. At lower doses, NE produced oxidative stress and a dose-dependent reduction of NE uptake activity without affecting cell viability significantly. Cu2+, which has no direct effect on NE uptake activity, potentiated oxidative stress and reduction of NE uptake activity produced by NE. This decrease of NE uptake activity was associated with reductions of NE uptake binding sites and NET protein expression by using the radioligand assay and Western blot analysis, but no changes in NET gene expression. In addition, the free-radical scavenger mannitol, and antioxidant enzymes superoxide dismutase and catalase, reduced oxidative stress and attenuated the reductions of NE uptake activity and NET protein produced by NE/Cu. Thus our results support a functional role of oxidative stress in mediating the neuronal NE uptake reducing effect of NE and that this effect of NE on NET is a posttranscriptional event.

Mareysemper I, Gelman M, Levistrauss M. 1993. The high-sensitivity to rotenone of striatal dopamine uptake suggests the existence of a constitutive metabolic deficiency in dopaminergic-neurons from the substantia-nigra. Eur J Neurosci 5(8):1029-1034.
Abstract: The toxicity of the 1-methyl-4-phenylpyridinium ion (MPP+), an inhibitor of complex I of the respiratory chain, on nigrostriatal dopaminergic neurons contrasts with its relative inefficiency towards other

catecholaminergic cell populations in spite of their ability to accumulate this neurotoxin through their high-affinity uptake system. A constitutive metabolic deficiency of the nigrostriatal dopaminergic neurons could account for their particular vulnerability to MPP+. In order to substantiate this hypothesis, we compared the inhibitory effects of rotenone, an inhibitor of mitochondrial oxidative phosphorylation, on the uptake of dopamine, serotonin, noradrenaline and GABA in mouse striatal synaptosomes, and of dopamine, serotonin and GABA in cultured mesencephalic neurons. In both preparations, the uptake of dopamine was much more affected than that of other neurotransmitters by rotenone. This result was confirmed using two other unrelated inhibitors of oxidative phosphorylation. Moreover, dopamine uptake in synaptosomes from the dorsolateral striatum was more sensitive to rotenone than uptake in synaptosomes from the nucleus accumbens. This indicates that intrinsic metabolic properties of the nigrostriatal dopaminergic neurons may explain the strong inhibition by rotenone of striatal dopamine uptake. Altogether, these results suggest that a constitutive metabolic deficiency could account, at least in part, for the selective vulnerability of the nigrostriatal dopaminergic pathway to the action of the neurotoxin MPP+.

Mareysemper I, Gelman M, Levistrauss M. 1995. A selective toxicity toward cultured mesencephalic dopaminergic-neurons is induced by the synergistic effects of energetic metabolism impairment and nmda receptor activation. J Neurosci 15(9):5912-5918.
Abstract: Numerous observations strongly support the hypothesis that dopaminergic neurons could be particularly vulnerable to an impairment of their energetic metabolism. In order to demonstrate the existence of such a selective vulnerability, the toxic effects of rotenone, an inhibitor of complex I of the respiratory chain, and of glutamate, which is very likely involved in the neurotoxicity induced by an energetic stress, were analyzed on cultured mouse mesencephalic neurons. Toxicity toward dopaminergic and GABAergic neurons was compared by measuring the residual uptakes of dopamine and GABA. Exposure to 5 nM rotenone for 6 hr or to a low concentration of glutamate (100 mu M) for 1 hr did not lead to a high selective toxic effect on dopaminergic neurons. In contrast, dopaminergic neurons were three times less resistant to the sequential exposure to rotenone and glutamate than GABAergic neurons. A particular resistance of mesencephalic GABAergic neurons to the synergistic toxic effects of rotenone and glutamate was ruled out since two other neuronal types, the striatal cholinergic and GABAergic neurons, displayed the same weak vulnerability as the mesencephalic GABAergic neurons. This selective toxic effect of glutamate on rotenone-pretreated dopaminergic neurons was blocked by either AMPA or NMDA receptor antagonists and mimicked by combined treatment with AMPA and NMDA, or by NMDA alone when the medium was deprived of Mg2+ ions. Moreover, this NMDA-selective neurotoxicity was critically dependent on the presence of a physiological extracellular sodium concentration, since the use of choline chloride instead of sodium chloride had a protective effect on dopaminergic neurons. Our results indicate that both the activation of NMDA receptors

and the impairment of the energetic metabolism induce a selective toxicity toward mesencephalic dopaminergic neurons. This could therefore explain their natural degeneration in the course of Parkinson's disease, in which mitochondrial abnormalities have been recently described.

Martin FL, Williamson SJM, Paleologou KE, Hewitt R, El-Agnaf OMA, Allsop D. 2003. Fe(II)-induced DNA damage in alpha-synuclein-transfected human dopaminergic BE(2)-M17 neuroblastoma cells: detection by the Comet assay. J Neurochem 87(3):620-630.
Abstract: Lewy bodies in the brains of patients with Parkinson's disease (PD) contain aggregates of alpha-synuclein (alpha-syn). Missense mutations (A53T or A30P) in the gene encoding alpha-syn are responsible for rare, inherited forms of PD. In this study, we explored the susceptibility of untransfected human dopaminergic BE(2)-M17 neuroblastoma cells, cells transfected with vector only, or cells transfected with wild-type alpha-syn, A30P alpha-syn or A53T alpha-syn to Fe(II)-induced DNA damage in the form of single-strand breaks (SSBs). DNA SSBs were detected following 2-h treatments with various concentrations of Fe(II) (0.01-100.0 mum), using the alkaline single cell-gel electrophoresis ('Comet') assay and quantified by measuring comet tail length (CTL) (mum). Fe(II) treatment induced significant increases in CTL in cells transfected with A30P alpha-syn or A53T alpha-syn, even at the lowest concentrations of Fe(II) tested. In comparison, untransfected cells, vector control cells or cells transfected with wild-type alpha-syn exhibited increases in SSBs only when exposed to concentrations of 1.0 mum Fe(II) and above. Even when exposed to higher concentrations (10.0-100.0 mum) of Fe(II), untransfected cells, vector control cells or cells transfected with wild-type alpha-syn were less susceptible to DNA-damage induction than cells transfected with A30P alpha-syn or A53T alpha-syn. Incorporation of DNA-repair inhibitors, hydroxyurea and cytosine arabinoside, enhanced the sensitivity of DNA damage detection. Susceptibility to Fe(II)-induced DNA damage appeared to be dependent on alpha-syn status because cells transfected with wild-type alpha-syn or A53T alpha-syn were equally susceptible to the damaging effects of the mitochondrial respiratory chain inhibitor rotenone. Overall, our data are suggestive of an enhanced susceptibility to the toxic effects of Fe(II) in neuroblastoma cells transfected with mutant alpha-syn associated with inherited forms of PD.

Maruyama W, Weinstock M, Youdim MBH, Nagai M, Naoi M. 2003. Anti-apoptotic action of anti-Alzheimer drug, TV3326 [(N-propargyl)(3R)-aminoindan-5-yl]-ethyl methyl carbamate, a novel cholinesterase-monoamine oxidase inhibitor. Neurosci Lett 341(3):233-236.
Abstract: The anti Parkinson drug, rasagiline [R-(+)-N-propargyl-1-aminoindan], an inhibitor of type B monoamine oxidase, has been shown to suppress apoptosis induced by neurotoxins and oxidative stress. A series of novel propargylaminoindans with a carbamate moiety to inhibit cholinesterase were developed from phamacophore of rasagiline to protect or rescue deteriorated neurons in Alzheimer's and Lewy Body disease and provide a beneficial effect on the cognitive deficits. Rasagiline analogues were found to protect dopaminergic SH-SY5Y cells against apoptosis

induced by peroxynitrite donor. SIN-1. TV3326, [(N-propargyl)-(3R)-aminoindan-5-yl]-ethyl methyl carbamate, was as effective as rasagiline in preventing apoptosis, followed by its S-enantiomer, TV3279. The anti-apoptotic-neuroprotective activity was shown to reside in the propargylamine and not the carbamate moiety. This resulted in stabilization of the mitochondrial membrane potential, the collapse of which initiates the apoptotic cascade. (C) 2003 Elsevier Science Ireland Ltd. All rights reserved.

Matesic DF, Blommel ML, Sunman JA, Cutler SJ, Cutler HG. 2001. Prevention of organochlorine-induced inhibition of gap junctional communication by chaetoglobosin K in astrocytes. Cell Biol Toxicol 17(6):395-408.
Abstract: Innumerable toxic substances present in the environment inhibit gap junctions, intercellular membrane channels that play fundamental roles in coordinated function of cells and tissues. Included are persistent organochlorine compounds, which pose health risks to humans and animals owing to their widespread use, bioaccumulation, and ability to inhibit gap junction channel-mediated intercellular communication in liver, lung, skin, heart, and brain cells. In this study, the organochlorine xenobiotics dieldrin and endosulfan, at micromolar concentrations, were found to inhibit gap junction-mediated intercellular communication and induce hypophosphorylation of connexin 43 in cultured rat astrocytes, the predominant cell type in the brain coupled through gap junctions. This inhibition of gap junctional communication was substantially reduced by preincubation with chaetoglobosin K (ChK), a bioactive natural produce previously shown to have ras tumor suppressor activity. Chaetoglobosin K also prevented dieldrin and endosulfan-induced hypophosphorylation of connexin 43 and prevented dieldrin-induced connexin 43 plaque dissolution in both astrocytes and cultured liver epithelial cells. The results suggest that stabilization of the native, phosphorylated form of connexin 43 by ChK may contribute to its ability to prevent organochlorine-induced inhibition of gap junction-mediated communication and dissolution of gap junction plaques within the plasma membrane.

Matsumura F. 2004. Contemporary issues on pesticide safety. Journal of Pesticide Science 29(4):299-303.
Abstract: At any given moment there are always new issues oil pesticide safety. Some of those issues are forced by the society based oil the emergence of new threats, the changing attitude of the general public or complaints by action groups representing special interests of certain sub-populations. Others are the results of new scientific dicoveries, technological development and/or introduction of new compounds. In this paper an effort has been made to analyze some of the recent issues from the viewpoint of categorizing them into several major types of safety issues in order to clarify the reason behind those issues, and thereby to assist the process of achieving the balance of effective use of pesticides and their safety. (C) Pesticide Science Society of Japan.

Mccann SJ, Lecouteur DG, Green AC, Brayne C, Johnson AG, Chan D, Mcmanus ME, Pond SM. 1998. The epidemiology of Parkinson's disease in an

Australian population. Neuroepidemiology 17(6):310-317.
Abstract: A prevalence study of Parkinson's disease (PD) was conducted in the rural town of Nambour, Australia. There were 5 cases of PD in a study population of 1207, yielding a crude prevalence ratio of 414 per 100,000 (95% confidence interval; 53-775). We performed a separate case-control study involving 224 patients with FD and 310 controls from South East Queensland and Central West New South Wales, to determine which factors increase the risk for PD in Australia. A positive family history of PD was the strongest risk factor for the development of the disease (odds ratio = 3.4; $p < 0.001$). In addition, rural residency was a significant risk factor for PD (odds ratio = 1.8, $p < 0.001$). Hypertension, stroke and well water ingestion were inversely correlated with the development of PD. There was no significant difference between patients and controls for exposure to herbicides and pesticides, head injury, smoking or depression. The high prevalence of PD in Nambour may be explained by rural residency. However, the most significant risk factor for PD was a positive family history. This demonstrates the need for improved understanding of the genetic nature of the disease.

Mccarthy S, Somayajulu M, Sikorska M, Borowy-Borowski H, Pandey S. 2004. Paraquat induces oxidative stress and neuronal cell death; neuroprotection by water-soluble Coenzyme Q(10). Toxicol Appl Pharmacol 201(1):21-31.
Abstract: Neuronal cell death induced by oxidative stress is correlated with numerous neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and stroke. The causes of sporadic forms of age-related neurodegenerative diseases are still unknown. Recently, a correlation between paraquat exposure and neurodegenerative diseases has been observed. Paraquat, a nonselective herbicide, was once widely used in North America and is still routinely used in Taiwan. We have used differentiated Human Neuroblastoma (SHSY-5Y) cells as an in vitro model to study the mechanism of cell death induced by paraquat. We observed that paraquat-induced oxidative stress in differentiated SHSY-5Y cells as indicated by an increase in the production of cellular reactive oxygen species (ROS). Furthermore, apoptosis was evident as indicated by cellular and nuclear morphology and DNA fragmentation. Interestingly, pretreatment of SHSY-5Y cells with water-soluble Coenzyme Q(10) (CoQ (10)) before paraquat exposure inhibited ROS generation. Pretreatment with CoQ(10) also significantly reduced the number of apoptotic cells and DNA fragmentation. We also analyzed the effect of paraquat and CoQ(10) on isolated mitochondria. Our results indicated that treatment with paraquat induced the generation of ROS from isolated mitochondria and depolarization of the inner mitochondrial membrane. Pretreatment with CoQ(10) was able to inhibit ROS generation from isolated mitochondria as well as the collapse of mitochondrial membrane potential. Our results indicate that water-soluble CoQ(10) can prevent oxidative stress and neuronal damage induced by paraquat and therefore, can be used for the prevention and therapy of neurodegenerative diseases caused by environmental toxins. (C) 2004 Elsevier Inc. All rights reserved.

Mccormack AL, Atienza JG, Johnston LC, Andersen JK, Vu S, Di Monte DA. 2005.

Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. J Neurochem 93(4):1030-1037.
Abstract: Systemic treatment of mice with the herbicide paraquat causes the selective loss of nigrostriatal dopaminergic neurons, reproducing the primary neurodegenerative feature of Parkinson's disease. To elucidate the role of oxidative damage in paraquat neurotoxicity, the time-course of neurodegeneration was correlated to changes in 4-hydroxy-2-nonenal (4-HNE), a lipid peroxidation marker. When mice were exposed to three weekly injections of paraquat, no nigral dopaminergic cell loss was observed after the first administration, whereas a significant reduction of neurons followed the second exposure. Changes in the number of nigral 4-HNE-positive neurons suggest a relationship between lipid peroxidation and neuronal death, since a dramatic increase in this number coincided with the onset and development of neurodegeneration after the second toxicant injection. Interestingly, the third paraquat administration did not cause any increase in 4-HNE-immunoreactive cells, nor did it produce any additional dopaminergic cell loss. Further evidence of paraquat-induced oxidative injury derives from the observation of nitrotyrosine immunoreactivity in the substantia nigra of paraquat-treated animals and from experiments with ferritin transgenic mice. These mice, which are characterized by a decreased susceptibility to oxidative stress, were completely resistant to the increase in 4-HNE-positive neurons and the cell death caused by paraquat. Thus, paraquat exposure yields a model that emphasizes the susceptibility of dopaminergic neurons to oxidative damage.

Mccormack AL, Di Monte DA. 2003. Effects of L-dopa and other amino acids against paraquat-induced nigrostriatal degeneration . J Neurochem 85(1): 82-86.
Abstract: Exposure to the herbicide paraquat causes selective nigrostriatal degeneration and aggregation of alpha-synuclein in the mouse brain. The purpose of this study was to assess mechanisms of paraquat entry into the CNS and, in particular, the effects of substrates of the blood-brain barrier (BBB) neutral amino acid transporter (System L carrier) on paraquat accumulation and neurotoxicity. Using a paraquat antibody, robust immunoreactivity was observed in the midbrain of mice injected with the herbicide. This immunoreactivity was abolished by administration of L-valine or L-phenylalanine, two System L substrates, immediately before paraquat exposure. Pre-treatment with these amino acids completely protected against paraquat-induced loss of nigrostriatal dopaminergic cells and formation of thioflavine S-positive intracellular deposits. Interestingly, the anti-parkinsonian drug L-dopa, which is transported across the BBB through the same neutral amino acid carrier, was also neuroprotective when administered 30 min prior to paraquat. In contrast, paraquat-induced toxicity was unaffected if animals (i) were pre-treated with d-valine, the biologically inactive d-isomer of L-valine, or with L-lysine, a substrate of the basic rather than the neutral amino acid carrier, or (ii) were injected with L-dopa 24 h after paraquat exposure. Data are consistent with a critical role of uptake across the BBB in paraquat neurotoxicity, and suggest that dietary elements (e.g. amino acids) or therapeutic agents

(e.g. L-dopa) may modify the effects of toxicants targeting the nigrostriatal system.

Mccormack AL, Thiruchelvam M, Manning-Bog AB, Thiffault C, Langston JW, Cory-Slechta DA, Di Monte DA. 2002. Environmental risk factors and Parkinson's disease: Selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis 10(2):119-127.
Abstract: Environmental toxicants and, in particular, pesticides have been implicated as risk factors in Parkinson's disease (PD). The purpose of this study was to determine if selective nigrostriatal degeneration could be reproduced by systemic exposure of mice to the widely used herbicide paraquat. Repeated intraperitoneal paraquat injections killed dopaminergic neurons in the substantia nigra (SN) pars compacta, as assessed by stereological counting of tyrosine hydroxylase (TH)-immunoreactive and Nissl-stained neurons. This cell loss was dose- and age-dependent. Several lines of evidence indicated selective vulnerability of dopaminergic neurons to paraquat. The number of GABAergic cells was not decreased in the SN pars reticulata, and counting of Nissl-stained neurons in the hippocampus did not reveal any change in paraquat-treated mice. Degenerating cell bodies were observed by silver staining, but only in the SN pars compacta, and glial response was present in the ventral mesencephalon but not in the frontal cortex and cerebellum. No significant depletion of striatal dopamine followed paraquat administration. On the other hand, enhanced dopamine synthesis was suggested by an increase in TH activity. These findings unequivocally show that selective dopaminergic degeneration, one of the pathological hallmarks of PD, is also a characteristic of paraquat neurotoxicity. The apparent discrepancy between pathological (i.e., neurodegeneration) and neurochemical (i.e., lack of significant dopamine loss) effects represents another important feature of this paraquat model and is probably a reflection of compensatory mechanisms by which neurons that survive damage are capable of restoring neurotransmitter tissue levels. (C) 2002 Elsevier Science (USA).

Mcdowell I, Hill G, Lindsay J, Helliwell B, Costa L, Beattie L, Hertzman C, Tuokko H, Gutman G, Parhad I, Parboosingh J, Bland R, Newman S, Dobbs A, Hazlett C, Rule B, Darcy C, Segall A, Chappell N, Manfreda J, Montgomery P, Ostbye T, Robertson J, Hachinski V, Chambers L, Munroeblum H, Eastwood R, Rifat S, Verdon J, Navarro J, Gauthier S, Wolfson C, Baumgarten M, Ska B, Joanette Y, Kergoat MJ, Nazerali N, Hebert R, Bravo G, Doyon J, Bouchard R, Morin J, Gauvreau D, Balram C, Rockwood K, Gray J, Fisk J, Nilsson T, Donald A, Buehler S, Prysephillips W, Kozma A. 1994. The canadian study of health and aging - risk-factors for alzheimers-disease in canada. Neurology 44( 11):2073-2080.
Abstract: Objective: To study risk factors for Alzheimer's disease (AD) based on data from the Canadian Study of Health and Aging. Design: Population-based case-control study. Setting: Communities and institutions in 10 Canadian provinces. Participants: Two hundred fifty-eight cases clinically diagnosed with probable AD, with onset of symptoms within 3 years of diagnosis, and 535 controls, frequency matched on age group, study center, and residence in community or institution, clinically confirmed

to be cognitively normal. Main outcome measure: Odds ratios (ORs) were calculated using unconditional logistic regression for previously hypothesized and potential risk factors for AD. Results: The OR for family history of dementia was significantly elevated (2.62; 95% confidence interval [CI], 1.53 to 4.51) and increased with the number of relatives with dementia. Those with less education were at higher risk of AD, with an OR of 4.00 (95% CI, 2.49 to 6.43) for those with 0 to 6 years, in comparison with those with 10 or more years. Head injury achieved borderline significance. A history of arthritis resulted in a low risk of AD (OR = 0.54; 95% CI, 0.36 to 0.81), as did a history of use of nonsteroidal anti-inflammatory drugs, Initial analyses showed an increased risk of AD for occupational exposure to glues as well as to pesticides and fertilizers; the increased risk was greater in those with less education. Conclusion: This study confirmed a number of previously reported risk factors for AD, but provided little support for others. A new finding was an increased risk for those with occupational exposure to glues as well as pesticides and fertilizers, but this needs further study.

Mcgrew DM, Irwin I, Langston JW. 2000. Ethylenebisdithiocarbamate enhances MPTP-induced striatal dopamine depletion in mice. Neurotoxicology 21(3): 309-312.
Abstract: Diethyldithiocarbamate (DDC) has been shown to enhance 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced striatal dopamine depletion in mice. Surprisingly, although DDC is a prototypic member of a class of compounds called dithiocarbamates (DTCs) that are widely used in industry and agriculture, only one study has investigated the interaction of dithiocarbamates other than DDC with MPTP. The purpose of the present study was to investigate whether two other widely used dithiocarbamates, ethylenebisdithiocarbamate (EBDC) and methyldithiocarbamate (MDC), would also enhance MPTP toxicity. The dithiocarbamates were administered to mice intraperitoneally at various doses with or without MPTP. Doses were chosen based on the LD50 values for each compound. DDC was also tested (using a previously reported dose) for comparison. Striata were obtained one week later for dopamine measurements. Consistent with previous reports, DDC produced statistically significant enhancement in MPTP-induced striatal dopamine depletion. EBDC also produced significant exacerbation of MPTP-induced dopamine depletion. In contrast to DDC and EBDC, MDC failed to enhance the effects of MPTP, even when administered at doses of high lethality. Further studies of the dithiocarbamate class of compounds may help to elucidate the mechanism of DDC and EBDC enhancement of MPTP toxicity. Given the widespread use of these compounds in the environment such studies may also provide clues to the process of nigrostriatal cell degeneration in Parkinson's disease. (C) 2000 Intox Press, Inc.

Mcnaught KS, Thull U, Carrupt PA, Altomare C, Cellamare S, Carotti A, Testa B, Jenner P, Marsden CD. 1996. Effects of isoquinoline derivatives structurally related to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on mitochondrial respiration. Biochem Pharmacol 51(11):1503-1511.
Abstract: Isoquinoline derivatives exert 1-methyl-4-phenylpyridinium (MPP

(+))-like activity as inhibitors of complex I and alpha-ketoglutarate dehydrogenase activity in rat brain mitochondrial fragments. We now examine the ability of 19 isoquinoline derivatives and MPP(+) to accumulate and inhibit respiration in intact rat liver mitochondria, assessed using polarographic techniques. None of the compounds examined inhibited respiration supported by either succinate + rotenone or tetramethylparaphenylenediamine (TMPD) + ascorbate. However, with glutamate + malate as substrates, 15 isoquinoline derivatives and MPP(+) inhibited state 3 and, to a lesser extent, state 4 respiration in a time-dependent manner. None of the isoquinoline derivatives were more potent than MPP(+). 6,7-Dimethoxy-1-styryl-3,4-dihydroisoquinoline uncoupled mitochondrial respiration. Qualitative structure activity relationship studies revealed that isoquinolinium cations were more active than isoquinolines in inhibiting mitochondrial respiration; these, in turn, were more active than dihydroisoquinolines and 1,2,3,4-tetrahydroisoquinolines. Three-dimensional quantitative structure activity relationship studies using Comparative Molecular Field Analysis showed that the inhibitory; potency of isoquinoline derivatives was determined by steric, rather than electrostatic, properties of the compounds. A hypothetical binding site was identified that may be related to a rate limiting transport process, rather than to enzyme inhibition. In conclusion, isoquinoline derivatives are less potent in inhibiting respiration in intact mitochondria than impairing complex I activity in mitochondrial fragments. This suggests that isoquinoline derivatives are not accumulated by mitochondria as avidly as MPP(+). The activity of charged and neutral isoquinoline derivatives implicates both active and passive processes by which these compounds enter mitochondria, although the quaternary nitrogen moiety of the isoquinolinium cations favours mitochondrial accumulation and inhibition of respiration. These findings suggest that isoquinoline derivatives may exert mitochondrial toxicity in vivo similar to that of MPTP/MPP(+).

Meco G, Bonifati V, Vanacore N, Fabrizio E. 1994. Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Scandinavian Journal of Work Environment & Health 20 (4):301-305.
Abstract: Permanent parkinsonism was observed in a man with chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Symptoms developed at 37 years of age, two years after exposure had ceased. To our knowledge, this is the second report on parkinsonism associated with exposure to maneb. Manganese is a well-known parkinsonigen toxin in humans. More recently, it has been shown that dithiocarbamates can also induce extrapyramidal syndromes. The biochemical effects of manganese and dithiocarbamates are reviewed and their possible neurotoxic mechanisms are discussed. Both of these components may have played a role in this case.

Menegon A, Board PG, Blackburn AC, Mellick GD, Le Couteur DG. 1998. Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet 352(9137):1344-1346.
Abstract: Background Parkinson's disease is thought to be secondary to

the presence of neurotoxins, and pesticides have been implicated as possible causative agents. Glutathione transferases (GST) metabolise xenobiotics, including pesticides. Therefore, we investigated the role of GST polymorphisms in the pathogenesis of idiopathic Parkinson's disease. Methods We genotyped by PCR polymorphisms in four GST classes (GSTM1, GSTT1, GSTP1, and GSTZ1) in 95 Parkinson's disease patients and 95 controls. We asked all patients for information about pesticide exposure. Findings The distribution of the GSTP1 genotypes differed significantly between patients and controls who had been exposed to pesticides (controls vs patients: AA 14 [54%] of 26 vs seven [18%] of 39; AB 11 [42%] of 26 vs 22 [56%] of 39; BE 1 [4%] of 26 vs six [15%] of 39; AC 0 vs four [10%] of 39, p=0.009). No association was found with any of the other GST polymorphisms. Pesticide exposure and a positive family history were risk factors for Parkinson's disease. Interpretation GSTP1-1, which is expressed in the blood-brain barrier, may influence response to neurotoxins and explain the susceptibility of some people to the parkinsonism-inducing effects of pesticides.

Menzies FM, Yenisetti SC, Min KT. 2005. Roles of Drosophila DJ-1 in survival of dopaminergic neurons and oxidative stress. Curr Biol 15(17):1578-1582. Abstract: The loss of dopaminergic neurons in the substantia nigra is the pathological hallmark of Parkinson's disease (PD). While the etiology of sporadic PD remains elusive, an inherited form of early-onset familial PD is linked to mutations of DJ-1 [1]. To understand the biological function of DJ-1 and its relevance to the pathogenesis of PD, we investigated the function of DJ-1 using Drosophila. Drosophila possesses two homologs of human DJ-1: DJ-1 alpha and DJ-1 beta. We found that DJ-1a is expressed predominantly in the testis, while DJ-1 beta is ubiquitously present in most tissues, resembling the expression pattern of human DJ-1. Loss-of-function DJ-1 beta mutants demonstrated an extended survival of dopaminergic neurons and resistance to paraquat stress, but showed acute sensitivity to hydrogen peroxide treatment. We showed a compensatory upregulation of DJ-1 alpha expression in the brain of the DJ-1 beta mutant and demonstrated that overexpression of DJ-1 alpha in dopaminergic neurons is sufficient to confer protection against paraquat insult. These results suggest that Drosophila homologs of DJ-1 play critical roles in the survival of dopaminergic neurons and response to oxidative stress.

Mercer LD, Kelly BL, Horne MK, Beart PM. 2005. Dietary polyphenols protect dopamine neurons from oxidative insults and apoptosis: investigations in primary rat mesencephalic cultures. Biochem Pharmacol 69(2):339-345. Abstract: Naturally occurring polyphenols have the potential to prevent oxidative damage in various pathophysiological conditions. Various members of the flavonoid family were investigated to determine if they could protect mesencephalic dopamine (DA) neurones from injury and reduce apoptosis produced by oxidative stressors. Primary mesencephalic cultures were sensitive to oxidative insults (hydrogen peroxide, 4-hydroxynonenal, rotenone, 6-hydroxydopamine and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium hydrochloride (MPP+)) which produced concentration-dependent decreases in cellular viability across an

apoptotic-necrotic continuum of injury. Flavonoids (catechin, quercetin, chrysin, puerarin, naringenin, genestein) protected mesencephalic cultures from injury by MPP+, which was shown by DNA fragmentation studies and tyrosine hydroxylase (TH) immunocytochemistry of DA neurones to occur by apoptosis. Catechin also reduced injury produced by hydrogen peroxide, 4-hydroxynonenal, rotenone and 6-hydroxydopamine as shown by increases in cellular viability and [H-3]DA uptake. When the neuroprotection of catechin against MPP+-induced injury was compared to that produced by the caspase-3 inhibitor, Z-DVED-FMK, both reduced DNA fragmentation and the injury patterns of TH-positive neurones. These data demonstrate the neuroprotective abilities of flavonoids which are able to attenuate the apoptotic injury of mesencephalic DA neurones. Since these DA neurones are under oxidative stress in Parkinsonism, our findings suggest that flavonoids could provide benefits along with other anti-oxidant therapies in Parkinson's disease. (C) 2004 Elsevier Inc. All rights reserved.

Messerli FH, Grossman E. 1998 Nov 12. The calcium antagonist controversy: a posthumous commentary. Am J Cardiol 82(9B):35R-39R.
Abstract: In 1995, some retrospective reports showed that certain patients treated with short-acting calcium antagonists were at increased risk for myocardial infarction and had a higher mortality rate compared with patients treated with other cardiovascular drugs. Subsequent reports attempted to establish a connection between calcium antagonists and disorders as diverse as malignancy, Parkinsonism, cognitive dysfunction, and suicide. However, other retrospective studies and, more compelling, several prospective studies have reported that calcium antagonists exert a beneficial effect on morbidity and mortality in a variety of cardiovascular disorders such as hypertension, ischemic heart disease after myocardial infarction, and congestive heart failure due to dilated cardiomyopathy. Calcium antagonists are a heterogeneous drug class, and distinct differences have been documented between short- and long-acting, as well as between dihydropyridine and nondihydropyridine, agents. Sympathetic activation, which is a risk factor for coronary events, occurs with short-acting agents only and is absent with long-acting calcium antagonists. Recent data make it extremely unlikely that calcium antagonists increase the risk of malignancy by affecting apoptosis or immunosuppression or both. Long-acting calcium antagonists have distinct benefits in patients with hypertension and diabetes and may be more beneficial than other drugs in patients with diabetes and left ventricular hypertrophy.

Messing B. 1991. Extrapyramidal disturbances after cyanide poisoning (first MRT-investigation of the brain). J Neural Transm Suppl 33:141-7.
Abstract: A 29 year old student of chemistry took 50 ml of a 1% potassium cyanide solution (500 mg) in attempted suicide. He became comatose, mydriatic and was admitted to hospital in an apneic state. He woke up after seven hours and developed Parkinsonism in the following weeks. This regressed slowly in the second month after the poisoning apart from dysarthria, bradykinesia of the upper limbs and very brisk monosynaptic reflexes. Three weeks after the intoxication, CCT was largely normal, and there was CSF-dense hypodensity in both putamina after five months.

Sharply delimited signal elevation in T2 corresponding to the two putamina was detected in the MRI eight weeks and five months after ingestion of the poison.

Meulener M, Whitworth AJ, Armstrong-Gold CE, Rizzu P, Heutink P, Wes PD, Pallanck LJ, Bonini NM. 2005. Drosophila DJ-1 mutants are selectively sensitive to environmental toxins associated with Parkinson's disease. Curr Biol 15(17):1572-1577.
Abstract: Parkinson's disease (PD) is a common neurodegenerative disorder that displays both sporadic and inherited forms [1]. Exposure to several common environmental toxins acting through oxidative stress has been shown to be associated with PD [2]. One recently identified inherited PD gene, DJ-1, may have a role in protection from oxidative stress [3-10], thus potentially linking a genetic cause with critical environmental risk factors. To develop an animal model that would allow integrative study of genetic and environmental influences, we have generated Drosophila lacking DJ-1 function. Fly DJ-1 homologs exhibit differential expression: DJ-1 0 is ubiquitous, while DJ-1 a is predominantly expressed in the male germline. DJ-1 alpha and DJ-1 beta double knockout flies are viable, fertile, and have a normal lifespan; however, they display a striking selective sensitivity to those environmental agents, including paraquat and rotenone, linked to PD in humans. This sensitivity results primarily from loss of DJ-1 beta protein, which also becomes modified upon oxidative stress. These studies demonstrate that fly DJ-1 activity is selectively involved in protection from environmental oxidative insult in vivo and that the DJ-1 beta protein is biochemically responsive to oxidative stress. Study of these flies will provide insight into the critical interplay of genetics and environment in PD.

Meyer MJ, Mosely DE, Amarnath V, Picklo MJ. 2004. Metabohom of 4-hydroxy-trans-2-nonenal by central nervous system mitochondria is dependent on age and NAD(+) availability. Chem Res Toxicol 17(9):1272-1279.
Abstract: Lipid peroxidation and mitochondrial dysfunction are associated with multiple neurodegenerative disorders including Alzheimer's disease and Parkinson's disease. 4-Hydroxy-trans-2-nonenal (HNE) is a major, neurotoxic product of lipid peroxidation whose levels are elevated in these diseases. Previous data from this laboratory demonstrate that mitochondria play an important role in the detoxification of HNE particularly through the oxidation of HNE to 4-hydroxy-trans-2-nonenoate (HNEAcid). In this work, we examined the disposition of HNE when incubated with intact, well-coupled, rat brain mitochondria. Our results demonstrated that HNE loss occurred in a time- and concentration-dependent, saturable manner with a Km of 28.0 +/- 11.8 muM HNE and a V-Max Of 10 +/- 1.7 nmol/min/mg. HNEAcid formation occurred in a saturable manner with a K-M of 25.3 +/- 6.3 muM HNE and a V-Max of 4.4 +/- 0.43 nmol/min/mg. The formation of HNE-glutathione adducts and HNE-protein adducts comprised only a small percentage of HNE consumption. HNE metabolism was significantly diminished in rat brain mitochondria isolated from older animals. We then tested the hypothesis that the mitochondrial NADH/NAD (+) ratio regulated matrix aldehyde dehydrogenase activity. Our results

demonstrate that HNE oxidation was significantly inhibited to a greater extent with pyruvate and malate as substrates vs succinate. Complex I inhibition with respiratory substrates further blocked HNE detoxification. Rotenone (100 nM) inhibited respiration by 15% whereas HNEAcid formation was decreased to 72% of control levels. These results demonstrate that in situ mitochondrial aldehyde detoxification is affected by decrements in NAD(+) availability and complex I activity.

Miller DB, Reinhard JF, Daniels AJ, Ocallaghan JP. 1991. Diethyldithiocarbamate potentiates the neurotoxicity of invivo 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and of invitro 1-methyl-4-phenylpyridinium. J Neurochem 57(2):541-549.
Abstract: Diethyldithiocarbamic acid (DDC) potentiates in vivo neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and in vitro neurotoxicity of 1-methyl-4-phenylpyridinium (MPP+). Male C57Bl/6 mice were given two or five injections of MPTP (30 mg/kg i.p.) preceded 0.5 h by DDC (400 mg/kg i.p.). The mice were tested for catalepsy, akinesia, or motor activity during and after the period of dosing. Striatal and hippocampal tissues were obtained at 2 and 7 days following the last injection and evaluated for dopamine and norepinephrine levels, respectively. These same tissues were also analyzed for the levels of glial fibrillary acidic protein (GFAP), an astrocyte-localized protein known to increase in response to neural injury. Pretreatment with DDC potentiated the effect of MPTP in striatum and resulted in substantially greater dopamine depletion, as well as a more pronounced elevation in GFAP. In hippocampus, the levels of norepinephrine and GFAP were not different from controls in mice receiving only MPTP, but pretreatment with DDC resulted in a sustained depletion of norepinephrine and an elevation of GFAP, suggesting that damage was extended to this brain area by the combined treatment. Mice receiving MPTP preceded by DDC also demonstrated a more profound, but reversible, catalepsy and akinesia compared to those receiving MPTP alone. Systemically administered MPP+ decreased heart norepinephrine, but did not alter the striatal levels of dopamine or GFAP, and pretreatment with DDC did not alter these effects, but did increase lethality. DDC is known to increase brain levels of MPP+ after MPTP, but our data indicate that this is not due to a movement of peripherally generated MPP+ into CNS. In cultured bovine adrenal medullary cells, MPP+ (300-mu-M) slightly decreased catecholamine levels, but had no effect on tyrosine hydroxylase activity or cellular protein. However, the incubation of these cells with both MPP+ and DDC (1.5 or 3.0 mM) caused large decreases in all indicators of cell viability. The enhancement of MPP+ neurotoxicity by DDC in an in vitro system, where distributional factors are limited, raises the possibility that mechanisms in addition to altered kinetics may account for DDC-induced potentiation of MPTP neurotoxicity in vivo.

Miller GW, Kirby ML, Levey AI, Bloomquist JR . 1999. Heptachlor alters expression and function of dopamine transporters. Neurotoxicology 20(4): 631-637.
Abstract: Epidemiological data support a relationship between pesticide

exposure and Parkinson's disease; however, no experimental evidence has been provided to support this association. Here we report that subchronic administration of the organochlorine insecticide heptachlor (0, 3, 6, 9, or 12 mg/kg given 3 times over a 2 week period) leads to a pronounced increase in both the plasma membrane transport of dopamine and the expression of the plasma membrane dopamine transporter (DAT), as well as the vesicular monoamine transporter (VMAT2) in the striatum of C57BL mice. To address possible mechanisms of increased DAT and VMAT2 expression, we performed transport studies in cell lines expressing the human forms of either DAT or VMAT2. In a DAT expressing cell line, acute treatment with the putative toxic species of heptachlor, heptachlor epoxide, did not alter plasma membrane dopamine uptake. In a VMAT2 expressing cell line, heptachlor epoxide significantly inhibited vesicular uptake of dopamine (45% reduction at 10 mu M). Since DAT has been proposed to be the molecular gateway for dopaminergic toxins, such as the parkinsonism-inducing neurotoxin MPP+, and VMAT2 has been proposed to protect cells from MPP+ and other toxins by sequestering the toxin into vesicles, the combined effects of heptachlor could increase the susceptibility of the nigrostriatal dopamine system to neurodegeneration. We further propose that altered dopamine transport by exposure to pesticides may provide a molecular basis for the increased incidence of Parkinson's disease. (C)1999 Inter Press, Inc.

Milusheva E, Baranyi M, Kittel A, Sperlagh B, Vizi ES. 2005. Increased sensitivity of striatal dopamine release to H2O2 upon chronic rotenone treatment. Free Radic Biol Med 39(1):133-142.
Abstract: It is believed that both mitochondrial dysfunction and oxidative stress play important roles in the pathogenesis of Parkinson's disease (PD). We studied the effect of chronic systemic exposure to the mitochondrial inhibitor rotenone on the uptake, content, and release of striatal neurotransmitters upon neuronal activity and oxidative stress, the latter simulated by H2O2 perfusion. The dopamine content in the rat striatum is decreased simultaneously with the progressive loss of tyrosine hydroxylase (TH) immunoreactivity in response to chronic intravenous rotenone infusion. However, surviving dopaminergic neurons take up and release only a slightly lower amount of dopamine (DA) in response to electrical stimulation. Striatal dopaminergic neurons showed increased susceptibility to oxidative stress by H2O2, responding with enhanced release of DA and with formation of an unidentified metabolite, which is most likely the toxic dopamine quinone (DAQ). In contrast, the uptake of [H-3]choline and the electrically induced release of acetylcholine increased, in coincidence with a decline in its D-2 receptor-mediated dopaminergic control. Thus, oxidative stress-induced dysregulation of DA release/uptake based on a mitochondrial deficit might underlie the selective vulnerability of dopaminergic transmission in PD, causing a self-amplifying production of reactive oxygen species, and thereby contributing to the progressive degeneration of dopaminergic neurons. (c) 2005 Elsevier Inc. All rights reserved.

Ming Z, Lu ZS, Gu JF, Sun LY, Liu XY. 2004. Co-treatment with ethanol enhances

the toxicity of 6-hydroxydopamine. Neurosci Lett 367(2):250-253.
Abstract: 6-Hydroxydopamine (6-OHDA) is a widely used neural toxin in the pathogenesis research of Parkinson's disease (PD). In this work, we have studied the effect of ethanol on the toxicity of 6-OHDA on PC12 cell and SK-N-SH cell. Ethanol alone had little toxicity to these cells. However, if using 40 muM 6-OHDA along with 400 mM ethanol on PC12 cell or SK-N-SH cell for 24 h, there was much more cell loss than using 40 muM 6-OHDA alone when detected by 3-(4,5-dimethylthiazal-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay or flow cytometric assay. The toxicity of 6-OHDA was enhanced only if using at least 200 mM ethanol, and the cell loss was increased with the increase of ethanol concentration. We had also found that ethanol could enhance the toxicity of 6-OHDA only when using ethanol and 6-OHDA at the same time, ethanol treatment either before or after 6-OHDA treatment did not show such effect. This effect of ethanol suggests that ethanol may contribute to the degeneration of dopaminergic cells. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Miranda-Contreras L, Davila-Ovalles R, Benitez-Diaz P, Pena-Contreras Z, Palacios-Pru E. 2005. Effects of prenatal paraquat and mancozeb exposure on amino acid synaptic transmission in developing mouse cerebellar cortex. Developmental Brain Research 160(1):19-27.
Abstract: The goal of this study was to analyze the effects of prenatal exposure to the pesticides paraquat (PQ) and mancozeb (MZ) on the development of synaptic transmission in mouse cerebellar cortex. Pregnant NMRI mice were treated with either saline, 10 mg/kg PQ 30 mg/kg MZ or the combination of PQ + MZ, between gestational days 12 (E12) and E20. Variation in the levels of amino acid neurotransmitters was determined by HPLC, between postnatal day 1 (P1) and P30. Motor coordination was assessed by locomotor activity evaluation of control and experimental pups at P14, P21 and P30. Significant reductions in the levels of excitatory neurotransmitters, aspartate and glutamate, were observed in PQ-, MZ- or combined PQ + MZ-exposed Pups, with respect to control, during peak periods of excitatory innervation of Purkinje cells: between P2-P5 and P11-P15. However, at P30, lower aspartate contents, in contrast with increased glutamate levels, were detected in all experimental groups. During the first two postnatal weeks, delays in GABA and glycine ontogenesis were observed in PQ- and PQ + MZ-exposed pups, whereas notable decrements in GABA and glycine levels were seen in PQ + MZ-exposed animals. Decreased taurine contents were detected at P3 and P11 in PQ- and PQ + MZ-exposed mice. Pups in different experimental groups all showed hyperactivity at P14 and then exhibited reduced locomotor activity at P30. Taken together, our results indicate that prenatal exposure to either PQ or MZ or the combination of both could alter the chronology and magnitude of synaptic transmission in developing mouse cerebellar cortex. (c) 2005 Published by Elsevier B.V.

Miyako K, Kai Y, Irie T, Takeshige K, Kang DC. 1997. The content of intracellular mitochondrial DNA is decreased by 1-methyl-4-phenylpyridinium ion (MPP (+)). J Biol Chem 272(15):9605-9608.
Abstract: 1-Methyl-4-phenylpyridinium ion (MPP(+)), an oxidative

metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is considered to be directly responsible for MPTP-induced Parkinson's disease-like symptoms by inhibiting NADH-ubiquinone oxidoreductase (complex I) in the mitochondrial respiratory chain, Here we demonstrate that 25 mu M MPP(+) decreases the content of mitochondrial DNA to about one-third in HeLa S3 cells, On the contrary, 0.1 mu M rotenone, which inhibits complex I to the same extent as 25 mu M MPP(+) in the cells, increases the content of mitochondrial DNA about a-fold, Hence, the effect of MPP(+) on mitochondrial DNA is not mediated by the inhibition of complex I, To examine the replication state of mitochondrial DNA, we measured the amount of nascent strands of mitochondrial DNA. The amount is decreased by MPP(+) but increased by rotenone, suggesting that the replication of mitochondrial DNA is inhibited by MPP(+). Because the proper amount of mitochondrial DNA is essential to maintain components of the respiratory chain, the decrease of mitochondrial DNA may play a role in the progression of MPTP induced Parkinson's disease-like symptoms caused by the mitochondrial respiratory failure.

Molina-Jimenez MF, Sanchez-Reus MI, Andres D, Cascales M, Benedi J. 2004. Neuroprotective effect of fraxetin and myricetin against rotenone-induced apoptosis in neuroblastoma cells. Brain Res 1009(1-2):9-16.
Abstract: Rotenone-induced apoptosis is considered to contribute to the etiology of Parkinson's disease (PD). We try to prevent the apoptosis induced by rotenone toxicity with 50 muM myricetin, 100 muM fraxetin and 100 muM N-acetylcysteine (NAC) that protect against reactive oxygen species (ROS), on SH-SY5Y human neuroblastoma cell line. Morphological changes induced by rotenone and intracellular ROS were assessed in live SH-SY5Y dopaminergic cells by confocal microscopy using the fluorescent dyes, dihydroethidium and 2',7'-dichlorofluorescein diacetate (DCFH-DA). DNA fragmentation was assayed as index of apoptosis. We also investigated oxidative stress parameters such as the glutathione redox status and lipid peroxidation. The exposure of the SH-SY5Y cells to rotenone 5 PM for 16 h produced severe morphological changes, DNA fragmentation and significative increases in the levels of hydrogen peroxide and superoxide anion. These increases were reduced by a 30-min pretreatment with fraxetin 100 muM or NAC 100 muM. DNA laddering produced by rotenone treatment was also inhibited by fraxetin and NAC. Treatment with 5 muM rotenone induced loss of reduced glutathione (GSH) and increased cellular levels of oxidized glutathione (GSSG). Fraxetin and NAC treatments restored glutathione redox ratio diminished after rotenone challenge and decreased the levels of lipid peroxidation. These results suggest that the natural antioxidants, such as fraxetin, may prevent the apoptotic death of dopaminergic cells induced by rotenone and mediated by oxidative stress. (C) 2004 Elsevier B.V. All rights reserved.

Molina-Jimenez MF, Sanchez-Reus MI, Benedi J . 2003. Effect of fraxetin and myricetin on rotenone-induced cytotoxicity in SH-SY5Y cells: comparison with N-acetylcysteine. Eur J Pharmacol 472(1-2):81-87.
Abstract: The purpose of this study was to investigate the potential neuroprotective effects of myricetin (flavonoid) and fraxetin (coumarin) on

rotenone-induced apoptosis in SH-SY5Y cells, and the possible signal pathway involved in a neuronal cell model of Parkinson's disease. These two compounds were compared to N-acetylcysteine. The viability of cells was assessed by 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and cytotoxicity was assayed by lactate dehydrogenase (LDH) released into the culture medium. Parameters related to apoptosis, such as caspase-3 activity, the cleavage of poly(ADP-ribose) polymerase and the levels of reactive oxygen species were also determined. Rotenone caused a time- and dose-dependent decrease in cell viability and the degree of LDH release was proportionally to the effects on cell viability. Cells were pretreated with ftaxetin, myricetin and N-acetylcysteine at different concentrations for 30 min before exposure to rotenone. Cytotoxicity of rotenone (5 muM) for 16 h was significantly diminished as well as the release of LDH into the medium, by the effect of fraxetin, myricetin and N-acetylcysteine, with fraxetin (100 muM) and N-acetylcysteine (100 muM) being more effective than myricetin (50 muM). Rotenone-induced apoptosis in SH-SY5Y cells was detected by an increase in caspase-3 activity and in the cleavage of poly(ADP-ribose) polymerase. After exposing these cells to rotenone, a significant increase in reactive oxygen species preceded apoptotic events. Fraxetin (100 muM) and N-acetylcysteme (100 muM) not only reduced rotenone-induced reactive oxygen species formation, but also attenuated caspase-3 activity and poly (ADP-ribose) polymerase cleavage at 16 h against rotenone-induced apoptosis. The effect of fraxetin in both experiments was similar to that of N-acetylcysteine. These results demonstrated the protective action of fraxetin and suggest that it can reduce apoptosis, possibly by decreasing free radical generation in SH-SY5Y cells. Myricetin at 100 muM was without any preventive effect. 

Molina-Jimenez MF, Sanchez-Reus MI, Cascales M, Andres D, Benedi J. 2005. Effect of fraxetin on antioxidant defense and stress proteins in human neuroblastoma cell model of rotenone neurotoxicity. Comparative study with myricetin and N-acetylcysteine. Toxicol Appl Pharmacol 209(3): 214-225.

Abstract: Mitochondrial complex I inhibitor rotenone induces apoptosis through enhancing mitochondrial reactive oxygen species production. Recently, it has been shown that fraxetin (coumarin) and myricetin (flavonoid) have significant neuroprotective effects against apoptosis induced by rotenone, increase the total glutathione levels in vitro, and inhibit lipid peroxidation. Thus, these considerations prompted us to investigate the way in which fraxetin and myricetin affect the endogenous antioxidant defense system, such as Mn and CuZn superoxide dismutase (MnSOD, CuZnSOD), catalase, glutathione reductase (GR), and glutathione peroxidase (GPx) on rotenone neurotoxicity in neuroblastoma cells. N-acetylcysteine (NAC), a potent antioxidant, was employed as a comparative agent. Also, the expression and protein levels of HSP70 by Northern and Western blot analysis were assayed in SH-SY5Y cells. After incubation for 16 h, rotenone significantly increased the expression and activity of MnSOD, GPx, and catalase. When cells were preincubated with

fraxetin, there was a decrease in the protein levels and activity of both MnSOD and catalase, in comparison with the rotenone treatment. The myricetin effect was less pronounced. Activity and expression of GPx were increased by rotenone and pre-treatment with fraxetin did not modify significantly these levels. The significant enhancement in HSP70 expression at mRNA and protein levels induced by fraxetin was observed by pre-treatment of cells 0.5 h before rotenone insult. These data suggest that major features of rotenone-induced neurotoxicity are partially mediated by free radical formation and oxidative stress, and that fraxetin partially protects against rotenone toxicity affecting the main protection system of the cells against oxidative injury. (c) 2005 Elsevier Inc. All rights reserved.

Mollace V, Iannone M, Muscoli C, Palma E, Granato T, Rispoli V, Nistico R, Rotiroti D, Salvemini D. 2003. The role of oxidative stress in paraquat-induced neurotoxicity in rats: protection by non peptidyl superoxide dismutase mimetic. Neurosci Lett 335(3 ):163-166.
Abstract: Herbicides, including paraquat, may produce neurodegenerative effect when given both peripherally and into the brain though the pathophysiological mechanism is still unknown. Microinfusion of paraquat into the Substantia Nigra (50 mug) produced increased motor activity, jumping and circling opposite to the injection site, associated with ECoG desynchronization, high voltage epileptogenic spikes, and with neuropathological effects. These effects were accompanied by increase of malondialdehyde (MDA) levels in the Substantia Nigra, suggesting that paraquat was able to induce oxidative stress when injected directly into the rat brain. Pre-treatment of rats with M40401, a non peptidyl superoxide dismutase (SOD) mimetic given directly into the Substantia Nigra or i.p. prevented both behavioural, electrocorticogram and neuropathological effects and MDA elevation. Taken together, these results demonstrate that paraquat produces brain damage via abnormal formation of oxygen free radicals and that this effect may be counteracted by novel SOD mimetics. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Monnier V, Girardot F, Audin W, Tricoire H. 2002. Control of oxidative stress resistance by IP3 kinase in Drosophila melanogaster. Free Radic Biol Med 33(9):1250-1259.
Abstract: Oxidative damage is thought to be a major causal factor of aging, and is implicated in several human pathologies such as Alzheimer's and Parkinson's diseases. Nevertheless the genetical determinants of in vivo oxidative stress response are still poorly understood. To identify cellular components whose deregulation leads to oxidative stress resistance, we performed a genetic screen in Drosophila melanogaster. We thus identified in this screen Drosophila Inositol 1,4,5-triphosphate kinase I (D-IP3K1), a Drosophila gene homologous to mammalian IP3Ks. In vertebrates, IP3Ks phosphorylate the second messenger Inositol 1,4,5-triphosphate (IP3) to produce Inositol 1,3,4,5 tetrakiphosphate (IP4). IP3 binding to its receptor (IP3R) triggers Ca2+ release from the endoplasmic reticulum (ER) to the cytosol, whereas IP4 physiological role remains elusive. We show here that ubiquitous overexpression of D-IP3K1 confers resistance of flies to H2O2- but not to paraquat-induced oxidative stress.

Additional genetic analysis with other members of IP3 and IP4 signaling pathways led us to propose that the D-IP3K1 protective effect is mainly mediated through the reduction of IP3 level (which probably results in reduced Ca2+ release from internal stores), rather than through the rise of IP4 level. (C) 2002 Elsevier Science Inc.

Montpied P, De Bock F, Rondouin G, Niel G, Briant L, Courseau AS, Lerner-Natoli M, Bockaert J. 2003. Caffeic acid phenethyl ester (CAPE) prevents inflammatory stress in organotypic hippocampal slice cultures. Molecular Brain Research 115(2):111-120.
Abstract: Caffeic acid phenethyl ester (CAPE) is an antioxidant component of propolis, a natural product secreted by honeybee. Recent literature shows that CAPE inhibits nuclear factor kappa B (NFkappaB) activation in cell lines. Since NFkappaB was shown to be a crucial factor in neuroinflammation and to be associated with some neuropathologies, CAPE might reduce these disorders in brain too and have therapeutic applications. To test this hypothesis we used a model of endotoxic insult (interferon-gamma, followed by lipopolysaccharide) on rat organotypic hippocampal cultures. Cerebral inflammatory responses were strongly inhibited by CAPE (100 muM): reductions of NFkappaB nuclear activity, tumor necrosis factor alpha and nitric oxide productions were observed. At the dose of maximal effects (100 muM), an increase of cAMP-responsive element binding protein (CREB) activity, which anti-inflammatory role is well known, was seen. We compared CAPE effects with those of other drugs: anti-inflammatory as acetyl-salicylate and dexamethasone (glucocorticoid), antioxidant as pyrrolidine dithiocarbamate, or selective permeant inhibitor of NFkappaB as SN 50 peptide. These studies lead us to conclude that CAPE presents an interesting and original neuropharmacological profile compared to these drugs and might be helpful in the prevention of neurotoxic events due to excessive inflammatory reaction in brain. CAPE interferes with several effectors of neuroinflammation that might have complementary and synergic effects and allows a rather durable control since an acute treatment at the time of endotoxin exposure allows to control inflammatory factors for over 48 h. (C) 2003 Elsevier B.V. All rights reserved.

Moon Y, Lee KH, Park JH, Geum D, Kim K. 2005. Mitochondrial membrane depolarization and the selective death of dopaminergic neurons by rotenone: protective effect of coenzyme Q(10). J Neurochem 93(5): 1199-1208.
Abstract: Chronic exposure to the pesticide rotenone induces a selective degeneration of nigrostriatal dopaminergic neurons and reproduces the features of Parkinson's disease in experimental animals. This action is thought to be relevant to its inhibition of the mitochondrial complex I, but the precise mechanism of this suppression in selective neuronal death is still elusive. Here we investigate the mechanism of dopaminergic neuronal death mediated by rotenone in primary rat mesencephalic neurons. Low concentrations of rotenone (5-10 nM) induce the selective death of dopaminergic neurons without significant toxic effects on other mesencephalic cells. This cell death was coincident with apoptotic events

including capsase-3 activation, DNA fragmentation, and mitochondrial membrane depolarization. Pretreatment with coenzyme Q(10), the electron transporter in the mitochondrial respiratory chain, remarkably reduced apoptosis as well as the mitochondrial depolarization induced by rotenone, but other free radical scavengers such as N-acetylcysteine, glutathione, and vitamin C did not. Furthermore, the selective neurotoxicity of rotenone was mimicked by the mitochondrial protonophore carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP), a cyanide analog that effectively collapses a mitochondrial membrane potential. These data suggest that mitochondrial depolarization may play a crucial role in rotenone-induced selective apoptosis in rat primary dopaminergic neurons.

Morano A, Jimenezjimenez FJ, Molina JA, Antolin MA. 1994. Risk-factors for parkinsons-disease - case-control study in the province of caceres, spain. Acta Neurol Scand 89(3):164-170.
Abstract: This case-control study, performed in a mixed rural and urban province, of 74 patients with Parkinson's disease (PD) and 148 unselected age and sex-matched controls, attempted to look possible risk factors for PD. Rural living, well-water drinking, positive family history for PD and postural tremor, were associated to an increased risk for PD, with results regarding exposure to pesticides near to statistical significance. Alcohol-drinking habit in males were associated to a decreased risk for PD, with results regarding cigarette-smoking habit in males near to statistical significance. We did not find association between the risk for PD and the following variables: 1)exposure to industrial toxins; 2) agricultural work; 3) cranial trauma; 4) previous common illnesses including some infections, arterial hypertension, diabetes mellitus, coronary heart disease and thyroid disease; 5) coffee and tea drinking habits.

Morikawa N, Nakagawahattori Y, Mizuno Y. 1996. Effect of dopamine, dimethoxyphenylethylamine, papaverine, and related compounds on mitochondrial respiration and complex I activity. J Neurochem 66(3): 1174-1181.
Abstract: We report the effect of papaverine, tetrahydro-papaverine, laudanosine, dimethoxyphenylethylamine, dopamine, and its metabolites on mitochondrial respiration and activities of the enzymes in the electron transfer complexes, as mitochondrial toxins may be implicated in the etiology and the pathogenesis of Parkinson's disease. Papaverine was the most potent inhibitor of complex and NADH-linked mitochondrial respiration among the compounds tested next to rotenone. Tetrahydropapaverine, dimethoxyphenylethylamine, and laudanosine also inhibited NADH-linked mitochondrial respiration and complex I activity in this order. Dopamine and its metabolites showed either no inhibition or only very weak inhibition. Compounds with dimethoxy residues in the phenyl ring were associated with more potent inhibition of complex I than those without. Our results warrant further studies on these and some related compounds as candidate neurotoxins causing Parkinson's disease.

Morioka N, Kumagai K, Morita K, Kitayama S, Dohi T. 2004. Nonsteroidal anti-inflammatory drugs potentiate 1-methyl-4-phenylpyridinium (MPP+)-

induced cell death by promoting the intracellular accumulation of MPP+ in PC12 cells. J Pharmacol Exp Ther 310(2):800-807.
Abstract: In this study, we investigated the effects of nonsteroidal anti-inflammatory drugs ( NSAIDs) on 1-methyl-4-phenylpyridinium (MPP+)-induced cell death in PC12 cells. Coincubation of PC12 cells with indomethacin, ibuprofen, ketoprofen, or diclofenac, but not aspirin or N-[2-(cyclohexyloxy)-4-nitrophenyl]methanosulfonamide (NS-398), significantly potentiated the MPP+-induced cell death. In contrast, these NSAIDs had no effect on rotenone-induced cell death. The potentiating actions of these NSAIDs were not suppressed by treatment with phenyl-N-butylnitrone, a radical scavenger; N-acetyl-L-cysteine, an antioxidant; Ac-DEVD-CHO, a selective caspase-3 inhibitor; or 2-chloro-5-nitro-N-phenylbenzamide (GW9662), a selective antagonist of peroxisome proliferator-activated receptor gamma. Furthermore, we observed that DNA fragmentation, which is one of the hallmarks of apoptosis, was not induced by coincubation with MPP+ and NSAIDs. We confirmed that coincubation of PC12 cells with 30 muM MPP+ and 100 muM indomethacin, ibuprofen, ketoprofen, or diclofenac led to a significant increase in the accumulation of intracellular MPP+ compared with incubation with 30 muM MPP+ alone. In addition, these NSAIDs markedly reduced the efflux of MPP+ from PC12 cells. (3-(3(2-(7-Chloro-2-quinolinyl)ethenyl)phenyl((3-dimethyl amino-3oxo-propyl) thio) methyl) propanoic acid (MK 571), which is an inhibitor of multidrug resistance proteins (MRPs), mimicked the NSAIDs-induced effects, increasing cell toxicity and promoting the accumulation of MPP+. Moreover, some types of MRPs' mRNA were detected in PC12 cells. These results suggest that some NSAIDs might cause a significant increase in the intracellular accumulation of MPP+ via the suppression of reverse transport by the blockade of MRP, resulting in the potentiation of MPP+-induced cell death.

Moses M, Johnson ES, Anger WK, Burse VW, Horstman SW, Jackson RJ, Lewis RG, Maddy KT, Mcconnell R, Meggs WJ, Zahm SH. 1993. Environmental equity and pesticide exposure. Toxicol Ind Health 9(5):913-959.
Abstract: Although people of color and low-income groups bear a disproportionate share of the health risks from exposure to pesticides, research attention has been meager, and data on acute and chronic health effects related to their toxic exposures are generally lacking. Increased resources are needed both to study this issue and to mitigate problems already identified. People of color should be a major research focus, with priority on long-term effects, particularly cancer, neurodevelopmental and neurobehavioral effects, long-term neurological dysfunction, and reproductive outcome. Suitable populations at high risk that have not been studied include noncertified pesticide applicators and seasonal and migrant farm workers, including children.

Mueller TH, Egensperger R, Moran L, Graeber MB. 2002. Transcriptome analysis of rotenone-inhibited rat dopaminergic neurons: implications for Parkinson's disease. Acta Neuropathol (Berl) 104( 5):563.

Muller-Mohnssen H, Hahn K. 1995 Apr. [A new method for early detection of

neurotoxic diseases (exemplified by pyrethroid poisoning)]. Gesundheitswesen 57(4):214-22.
Abstract: This pilot-study should contribute to the question whether Pyrethroid intoxication can be distinguished from other diseases by characteristic clinical symptoms. The results show that the characteristics of the intoxication do not consist in singular symptoms but in combinations and correlations of symptoms, i.e. of central-neurological with peripheral- and autonomic-neurological as well as with characteristic immunological disturbances. Neurological symptoms consist in cerebro-organic disfunctions, locomotory disorders reminiscent of multiple sclerosis or M. Parkinson, and sensory, motoric and vegetative polyneuropathy, leading, for instance, to cardiovascular regulatory disorder like sympathicotonia or, orthostatic hypotonia. Non-neurological symptoms include immunosuppression with consecutive opportunistic infections, like candida albicans, most frequently of the alimentary tract, but also dermal and mucosal swellings, lichen-ruber-like efflorescences, loss of hair, conjunctivitis. Other symptoms are: hypoglycaemic crises inhibition of fertility, disturbances of blood clotting, and most frequently in children, suspected hematopoetic disorders.

Muller-Vahl KR, Kolbe H, Dengler R. 1999. Transient severe parkinsonism after acute organophosphate poisoning. J Neurol Neurosurg Psychiatry 66(2): 253-254.

Munishkina LA, Cooper EM, Uversky VN, Fink AL. 2004. The effect of macromolecular crowding on protein aggregation and amyloid fibril formation. J Mol Recognit 17(5):456-464.
Abstract: Macromolecular crowding is expected to have several significant effects on protein aggregation; the major effects will be those due to excluded volume and increased viscosity. In this report we summarize data demonstrating that macromolecular crowding may lead to a dramatic acceleration in the rate of protein aggregation and formation of amyloid fibrils, using the protein a-synuclein. The aggregation of a-synuclein has been implicated as a critical factor in development of Parkinson's disease. Various types of polymers, from neutral polyethylene glycols and polysaccharides (Ficolls, dextrans) to inert proteins, are shown to accelerate a-synuclein fibrillation. The stimulation of fibrillation increases with increasing length of polymer, as well as increasing polymer concentration. At lower polymer concentrations (typically up to similar to100mg/ml) the major effect is ascribed to excluded volume, whereas at higher polymer concentrations evidence of opposing viscosity effects become apparent. Pesticides and metals, which are linked to increased risk of Parkinson's disease by epidemiological studies, are shown to accelerate alpha-synuclein fibrillation under conditions of molecular crowding. Copyright (C) 2004 John Wiley Sons, Ltd.

Muralikrishnan D, Ebadi M, Brown-Borg HM. 2002. Effect of MPTP on dopamine metabolism in Ames dwarf mice. Neurochem Res 27(6):457-464.
Abstract: Hypopituitary dwarf mice exhibit a heightened antioxidative capacity and live extensively longer than age-matched controls.

Importantly, dwarf mice resist peripheral oxidative stress induced by paraquat, and behaviorally, they maintain cognitive function and locomotor activity at levels above those observed in old wild-type animals. We assessed monoaminergic neurotransmitters in nigrostriatal tract and cerebellum after the administration of the dopaminergic neurotoxin, MPTP. There was no significant change in mitochondrial monoamine oxidase (MAO)-B and total MAO activity in the substantia nigra and nucleus caudatus putamen of wild-type and dwarf mice. Coenzymes Q-9 and Q-10 were present in similar quantities, as were dopamine, norepinephrine, and serotonin levels in the cerebellum and nigrostriatal tract. MPTP set off tremor, hind limb abduction, and straub tail behavior and induced significant dopamine depletion in the striatum of both dwarf and normal mice. This study shows that the MAO activity and the coenzyme content of dwarf mice are similar to those of their wild-type controls and hence susceptible to MPTP-induced toxicity.

Nagao M, Takatori T, Inoue K, Shimizu M, Terazawa K. 1991. Immunohistochemical localization of paraquat in lungs and brains. Acs Symposium Series 451:264-271.
Abstract: Immunohistochemistry was used to investigate the localization and dynamics of paraquat in lung and brain in paraquat-poisoned rats. Rats were sacrificed at 3 h, 12 h, 24 h, 3 days, 7 days and 10 days after the intravenous injection of paraquat (5 mg/kg). In lung tissues, paraquat was localized in walls of blood vessels and bronchiolar epithelial cells from 3 h to 10 days after the paraquat exposure. Furthermore, histiocytes containing paraquat were observed. Interstitial pulmonary fibrosis containing paraquat developed with time. These results indicate that histiocytes are the probable cause of the pulmonary fibrosis in paraquat-poisoned rats. On the other hand, in brain tissues, paraquat was localized only in capillary walls and glial cells but was not observed in nerve cells 10 days after the injection of paraquat, providing evidence that paraquat cannot pass through the blood-brain barrier.

Nakamura K, Bindokas VP, Kowlessur D, Elas M, Milstein S, Marks JD, Halpern HJ, Kang UJ. 2001. Tetrahydrobiopterin scavenges superoxide in dopaminergic neurons. J Biol Chem 276(37):34402-34407.
Abstract: Increased oxidative stresses are implicated in the pathogenesis of Parkinson's disease, and dopaminergic neurons may be intrinsically susceptible to oxidative damage. However, the selective presence of tetrahydrobiopterin (BH4) makes dopaminergic neurons more resistant to oxidative stress caused by glutathione depletion. To further investigate the mechanisms of BH4 protection, we examined the effects of BH4 on superoxide levels in individual living mesencephalic neurons. Dopaminergic neurons have intrinsically lower levels of superoxide than nondopaminergic neurons. In addition, inhibiting BH4 synthesis increased superoxide in dopaminergic neurons, while BH4 supplementation decreased superoxide in nondopaminergic cells. BH4 is also a cofactor in catecholamine and NO production. In order to exclude the possibility that the antioxidant effects of BH4 are mediated by dopamine and NO, we used fibroblasts in which neither catecholamine nor NO production occurs. In fibroblasts, BH4

decreased baseline reactive oxygen species, and attenuated reactive oxygen species increase by rotenone and antimycin A. Physiologic concentrations of BH4 directly scavenged superoxide generated by potassium superoxide in vitro. We hypothesize that BH4 protects dopaminergic neurons from ordinary oxidative stresses generated by dopamine and its metabolites and that environmental insults or genetic defects may disrupt this intrinsic capacity of dopaminergic neurons and contribute to their degeneration in Parkinson's disease.

Nakamura K, Bindokas VP, Marks JD, Wright DA, Frim DM, Miller RJ, Kang UJ. 2000. The selective toxicity of 1-methyl-4-phenylpyridinium to dopaminergic neurons: The role of mitochondrial complex I and reactive oxygen species revisited. Mol Pharmacol 58(2):271-278.
Abstract: 1-Methyl-4-phenylpyridinium (MPP+) is selectively toxic to dopaminergic neurons and has been studied extensively as an etiologic model of Parkinson's disease (PD) because mitochondrial dysfunction is implicated in both MPP+ toxicity and the pathogenesis of PD. MPP+ can inhibit mitochondrial complex I activity, and its toxicity has been attributed to the subsequent mitochondrial depolarization and generation of reactive oxygen species. However, MPP+ toxicity has also been noted to be greater than predicted by its effect on complex I inhibition or reactive oxygen species generation. Therefore, we examined the effects of MPP+ on survival, mitochondrial membrane potential (Delta Psi m), and superoxide and reduced glutathione levels in individual dopaminergic and nondopaminergic mesencephalic neurons. MPP+ (5 mu M) selectively induced death in fetal rat dopaminergic neurons and caused a small decrease in their Delta Psi m. In contrast, the specific complex I inhibitor rotenone, at a dose (20 nM) that was less toxic than MPP+ to dopaminergic neurons, depolarized Delta Psi m to a greater extent than MPP+. In addition, neither rotenone nor MPP+ increased superoxide in dopaminergic neurons, and MPP+ failed to alter levels of reduced glutathione. Therefore, we conclude that increased superoxide and loss of Delta Psi m may not represent primary events in MPP+ toxicity, and complex I inhibition alone is not sufficient to explain the selective toxicity of MPP+ to dopaminergic neurons. Clarifying the effects of MPP+ on energy metabolism may provide insight into the mechanism of dopaminergic neuronal degeneration in PD.

Nakao N, Nakai K, Itakura T. 1997. Metabolic inhibition enhances selective toxicity of L-DOPA toward mesencephalic dopamine neurons in vitro. Brain Res 777(1-2):202-209.
Abstract: Recent in vitro studies have described the toxicity of levodopa (L-DOPA) to dopamine (DA) neurons. We investigated whether metabolic inhibition with rotenone, an inhibitor of complex I of the mitochondrial respiratory chain, may enhance the toxicity of L-DOPA toward DA neurons in mesencephalic cultures. The uptakes of DA and GABA were determined to evaluate the functional and morphological integrity of DA and non-DA neurons, respectively. Pretreatment with rotenone significantly augmented the toxic effect of L-DOPA on DA neurons. Interestingly, prior metabolic inhibition with rotenone rendered DA cells susceptible to a dose (5 mu M) of L-DOPA that otherwise exhibited no toxic effect. DA uptake was more

intensely attenuated than GABA uptake after the combined exposure to rotenone and L-DOPA. This was confirmed by cell survival estimation showing that tyrosine hydroxylase-positive DA cells are more vulnerable to the sequential exposure to the drugs than total cells. The selective toxic effect of L-DOPA on rotenone-pretreated DA neurons was significantly blocked by antioxidants, but not antagonists of NMDA or non-NMDA glutamate receptors. This indicates that oxidative stress play a central role in mediating the selective damage of DA cells in the present experimental paradigm. Our results raise the possibility that long-term L-DOPA treatment could accelerate the progression of degeneration of DA neurons in patients with Parkinson's disease where potential energy failure due to mitochondrial defects has been demonstrated to take place. (C) 1997 Elsevier Science B.V.

Naoi M, Maruyama W, Shamoto-Nagai M, Yi H, Akao Y, Tanaka M. 2005. Oxidative stress in mitochondria - Decision to survival and death of neurons in neurodegenerative disorders. Mol Neurobiol 31(1-3):81-93. Abstract: In mitochondria, oxidative phosphorylation and enzymatic oxidation of biogenic amines by monoamine oxidase produce reactive oxygen and nitrogen species, which are proposed to cause neuronal cell death in neurodegenerative disorders, including Parkinson's and Alzheimer's disease. In these disorders, mitochondrial dysfunction, increased oxidative stress, and accumulation of oxidation-modified proteins are involved in cell death in definite neurons. The interactions among these factors were studied by use of a peroxynitrite-generating agent, N-morpholino sydnonimine (SIN-1) and an inhibitor of complex 1, rotenone, in human dopaminergic SH-SY5Y cells. In control cells, peroxynitrite nitrated proteins, especially the subunits of mitochondrial complex I, as 3-nitrotyrosine, suggesting that neurons are exposed to constant oxidative stress even under physiological conditions. SIN-1 and an inhibitor of proteasome, carbobenzoxy-L-isoleucyl-gamma-t-butyl-L-alanyl-L-leucinal (PSI), increased markedly the levels of nitrated proteins with concomitant induction of apoptosis in the cells. Rotenone induced mitochondrial dysfunction and accumulation and aggregation of proteins modified with acrolein, an aldehyde product of lipid peroxidation in the cells. At the same time, the activity of the 20S beta-subunit of proteasome was reduced significantly, which degrades oxidative-modified protein. The mechanism was proved to be the result of the modification of the 20S beta-subunit with acrolein and to the binding of other acrolein-modified proteins to the 20S beta-subunit. Increased oxidative stress caused by SIN-1 treatment induced a decline in the mitochondrial membrane potential, Delta Psi m, and activated mitochondrial apoptotic signaling and induced cell death in SH-SY5Y cells. As another pathway, p38 mitogen-activated protein (MAP) kinase and exracellular signal-regulated kinase (ERK) mediated apoptosis induced by SIN-1. On the other hand, a series of neuroprotective propargylamine derivatives, including rasagiline [N-propargyl-1(R) aminoindan] and (-)deprenyl, intervened in the activation of apoptotic cascade by reactive oxygen species-reactive nitrogen species in mitochondria through stabilization of the membrane potential, Delta Psi m.

In addition, rasagiline induced antiapoptotic Bcl-2 and glial cell line-derived neurotrophic factor (GDNF) in SH-SY5Y cells, which was mediated by the ERK-nuclear factor (NF)-kappa B pathway. These results are discussed in relation to the interaction of oxidative stress and mitochondria in the regulation of neuronal death and survival in neurodegenerative diseases.

Naylor JL, Widdowson PS, Simpson MG, Farnworth M, Ellis MK, Lock EA. 1995. Further evidence that the blood-brain-barrier impedes paraquat entry into the brain. Human & Experimental Toxicology 14(7):587-594.
Abstract: The distribution of the non-selective herbicide paraquat was examined in the brain following subcutaneous administration of 20 mg kg (-1) paraquat ion containing [C-14]paraquat to male adult rats in order to determine whether paraquat crosses the blood/brain barrier. Following administration, [C-14]paraquat reached a maximal concentration in the brain (0.05% of administered dose) within the first hour and then rapidly disappeared from the brain. However, 24 h alter administration of the herbicide, about 13% of the maximal recorded concentration of paraquat remained in the brain (1.6 nnol g(-1) wet weight) and could not be removed by intracardiac perfusion. Using measurements of [C-14]paraquat in dissected brain regions and using quantitative autoradiography we demonstrated an asymmetrical distribution in and around the brain at 30 min (maximal concentration) and 24 h after administration. Most of the paraquat was associated with five structures, two of which, the pineal gland and linings of the cerebral ventricles lie outside the blood/brain barrier whilst the remaining three brain areas, the anterior portion of the olfactory bulb, hypothalamus and area postrema do not have a blood/brain barrier. Overall, the distribution of [C-14]paraquat in the brain 24 h after systemic administration was highly correlated to the blood volume. These data indicate that any remaining paraquat in the brain 24 h after systemic administration is associated with elements of the cerebro-circulatory system, such as the endothelial cells that make up the capillary network and that there is a limited entry of paraquat into brain regions without a blood/brain barrier. No [C-14]paraquat was detected in regions where there has been demonstrated pathology in brains from humans with Parkinson's disease. Finally, we could find no evidence for paraquat-induced neuronal cell necrosis 24 or 48 h after systemic administration. Overall it may be concluded that systemically administered paraquat does not pose a direct major neurotoxicological risk in the majority of brain regions which have a functional blood/brain barrier since paraquat can be excluded from the brain by this barrier.

Nelson LM, Van Den Eeden SK, Tanner CM, Efird JT, Bernstein AL. 2000. Home pesticide exposure and the risk of Parkinson's disease. Neurology 54 (7):A472-A473.

Newhouse K, Hsuan SL, Chang SH, Cai BB, Wang YP, Xia ZG. 2004. Rotenone-induced apoptosis is mediated by p38 and JNK MAP kinases in human dopaminergic SH-SY5Y cells. Toxicol Sci 79(1):137-146.
Abstract: Rotenone is a naturally derived pesticide that has recently been shown to evoke the behavioral and pathological symptoms of Parkinson's

disease in animal models. Though rotenone is known to be an inhibitor of the mitochondrial complex I electron transport chain, little is known about downstream pathways leading to its toxicity. We used human dopaminergic SH-SY5Y cells to study mechanisms of rotenone-induced neuronal cell death. Our results suggest that rotenone, at nanomolar concentrations, induces apoptosis in SH-SY5Y cells that is caspase-dependent. Furthermore, rotenone treatment induces phosphorylation of c-Jun, the c-Jun N-terminal protein kinase (JNK), and the p38 mitogen activated protein (MAP) kinase, indicative of activation of the p38 and JNK pathways. Importantly, expression of dominant interfering constructs of the JNK or p38 pathways attenuated rotenone-induced apoptosis. These data suggest that rotenone induces apoptosis in the dopaminergic SH-SY5Y cells that requires activation of the JNK and p38 MAP kinases and caspases. These studies provide insights concerning the molecular mechanisms of rotenone-induced apoptosis in neuronal cells.

Nieto M, Gil-Bea FJ, Dalfo E, Cuadrado M, Cabodevilla F, Sanchez B, Catena S, Sesma T, Ribe E, Ferrer I, Ramirez MJ, Gomez-Isla T. 2005 Jul 7. Increased sensitivity to MPTP in human alpha-synuclein A30P transgenic mice. Neurobiol Aging .
Abstract: In addition to genetic factors, environmental factors have long been suspected to contribute to the pathogenesis of Parkinson's disease (PD). We investigated the possible interaction between genetic factors and neurotoxins by testing whether alpha-synuclein A30P Tg5093 transgenic mice show increased sensitivity to secondary toxic insults like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or rotenone. While sensitivity to chronic treatment with rotenone was not enhanced in the Tg5093 line, chronic treatment with 80 or 150mg/kg MPTP resulted in increased deterioration of the nigrostriatal dopaminergic system as assessed by quantitation of nigral tyrosine hydroxylase (TH) positive neurons and striatal dopamine (DA) levels in Tg5093 mice when compared to non-transgenic littermate controls. Thus, the results of this study demonstrate a role for the overexpression of mutant human alpha-synuclein A30P in increased vulneravility of DA neurons to MPTP.

Noh JS, Kim EY, Kang JS, Kim HR, Oh YJ, Gwag BJ. 1999. Neurotoxic and neuroprotective actions of catecholamines in cortical neurons. Exp Neurol 159(1):217-224.
Abstract: We examined the possibility that catecholamines (CA) could act as endogenous modulators of neuronal death. Exposure to high doses (>100 mu M) of dopamine (DA) caused widespread neuronal death within 24 h in mouse cortical cell cultures and was accompanied by cell body shrinkage, aggregation and condensation of nuclear chromatin, and prominent internucleosomal DNA fragmentation. Epinephrine, but not norepinephrine (NE), was slightly toxic to neurons at doses higher than 1 mM. DA-induced death was attenuated by the addition of three different anti-apoptosis agents, 1 mu g/ml cycloheximide, 25 mM K+, or 100 ng/ml brain-derived neurotrophic factor (BDNF). While treatment with 100 mu M N-acetyl-L-cysteine attenuated DA neurotoxicity, neither the glutamate antagonists (10 mu M MK-801 plus 50 mu M CNQX) nor several

antioxidants [trolox, 100 mu M; Mn (III) tetrakis (4-benzoic acid) porphyrin chloride, 100 mu M; Mn (III) tetrakis (1-methyl-4pyridyl) prophyrin pentachloride, 100 mu M; N-tert-butyl-alpha-phenylnitrone, 3 mM] prevented the CA-induced apoptosis. Interestingly, all CA at 1-30 mu M attenuated free radical-mediated neuronal necrosis following exposure to 30 mu M Fe2+ or 200 mu M H2O2, which was insensitive to DA or NE antagonists. Like trolox, CA reduced levels of the stable free radical 1,1-diphenyl-2-picrylhydrazyl under cell-free conditions, raising the possibility that CA as an antioxidant protects neurons. We also found that the neuroprotective effect of CA prolonged the protective effects of BDNF against serum deprivation, The present findings suggest that CA induces apoptosis at high doses but prevents free radical-mediated neurotoxicity as an anti-oxidant without being coupled to the receptors. (C) 1999 Academic Press.

Nunes MV, Tajara EH. 1998. Delayed effects of organochlorine pesticides in man. Rev Saude Publica 32(4):372-382.
Abstract: Available information on organochlorines and the chronic effects of exposure to them are set out. Organochlorinated compounds are the most persistent pesticides and can be found in all ecosystems. Although they are generally efficient in pest control, they are also a potent environment pollutant and can provoke health problems in man. The evidences of the carcinogenic potential of organochlorines are controversial and insufficient, but they have been related to an increase in the incidence of some kinds of tumors, such as leukemia and solid tumours. Reproductive effects, due to anti-androgenic and estrogenic action, on embryonic virilization, the incidence of abortion and the frequency of prematurity, have also been observed. The accumulation of the organochlorines in the adipous tissue is positively correlated to the increase in aging and could be implicated in the development of aging diseases, such as Parkinson's disease. The effects of pesticide on human health have not yet been completely elucidated. Genotoxicity is one of the most serious of the possible harmful effects caused by these compounds and calls for special attention in view of the irreversible nature of the process and to the long latency associated with its manifestation.

Nuti A, Ceravolo R, Dell'agnello G, Gambaccini G, Bellini G, Kiferle L, Rossi C, Logi C, Bonuccelli U. 2004. Environmental factors and Parkinson's disease: a case-control study in the Tuscany region of Italy. Parkinsonism & Related Disorders 10(8):481-485.
Abstract: To date the aetiology of Parkinson's disease (PD) is unknown although both genetic susceptibility and environmental factors appear to play an important role in the development of the disease. Recent data have also indicated that chronic exposure to a common pesticide can reproduce the neurochemical, behavioral and neuropathological features of PD. The epidemiological studies previously carried on the prevalence of PD in population exposed to environmental factors have produced controversial results, probably because of different trial design and different analysis methods. A case-control retrospective study was conducted in a well-defined geographic area in Tuscany-Italy with the aim

to identify environmental factors possibly related to PD. No significant difference between PD patients and control subjects was observed in time spent in rural or industrial residence, in well water drinking and in the exposure to herbicides and pesticides. A significant difference between patients with PD and controls was reported for cigarette smoking, controls resulting more likely cigarette smokers in comparison with PD patients. The present findings support the view of a protective effect of cigarette smoking and do not show any significant association between environmental factors and the risk of development of PD. (C) 2004 Elsevier Ltd. All rights reserved.

Ogawa N, Asanuma M, Miyazaki I, Diaz-Corrales FJ, Miyoshi K. 2005. L-DOPA treatment from the viewpoint of neuroprotection - Possible mechanism of specific and progressive dopaminergic neuronal death in Parkinson's disease. J Neurol 252:23-31.
Abstract: With regard to the mechanism of selective dopaminergic neuronal death, experimental results of studies on the neurotoxicity of MPTP and rotenone indicate that degeneration of dopamine neurons is closely related to mitochondrial dysfunction, inflammatory process and oxidative stress, particularly with regard to the generation of quinones as dopamine neuron-specific oxidative stress. Thus, it is now clear that the presence of high levels of discompartmentalized free dopamine in sdopaminergic neurons may explain the specific vulnerability of dopaminergic neurons through the generation of highly toxic quinones.

Ogawa N, Asanuma M, Miyazaki I, Diaz-Corrales FJ, Miyoshi K. 2005 Oct. L-DOPA treatment from the viewpoint of neuroprotection. Possible mechanism of specific and progressive dopaminergic neuronal death in Parkinson's disease. J Neurol 252 Suppl 4:IV23-IV31.
Abstract: With regard to the mechanism of selective dopaminergic neuronal death, experimental results of studies on the neurotoxicity of MPTP and rotenone indicate that degeneration of dopamine neurons is closely related to mitochondrial dysfunction, inflammatory process and oxidative stress, particularly with regard to the generation of quinones as dopamine neuron-specific oxidative stress. Thus, it is now clear that the presence of high levels of discompartmentalized free dopamine in dopaminergic neurons may explain the specific vulnerability of dopaminergic neurons through the generation of highly toxic quinones.

Ogawa N, Asanuma M, Miyoshi K. 2004 Sep. [Mechanism of specific dopaminergic neuronal death in Parkinson's disease]. Nippon Rinsho 62(9):1629-34.
Abstract: Parkinson's disease (PD) is characterized by progressive degeneration of dopaminergic (DAergic) neurons of the nigrostriatal system, with resulting reduction in striatal dopamine (DA) concentration. Various mechanisms have been implicated in the pathogenesis and progression of PD. Among them, mitochondrial dysfunction, inflammation and oxidative stress had been accepted as the most plausible mechanism of disease progression. The free radicals/oxidative stress produced by MPTP, 6-hydroxydopamine, rotenone, activated microglias, and disturbances in mitochondrial respiratory enzymes provide a common

pathway for the progression of all kinds of neurons. On the other hand, numerous studies on DA-induced neurotoxicity have been reported recently, and DA itself exerts cytotoxicity in DAergic neurons mainly due to the generation of highly reactive DA -quinones which are DAergic neuron-specific cytotoxic molecules. DA quinones may irreversibly alter protein function through the formation 5-cysteinyl-dopamine on the protein. For example, the formation of DA quinone-alpha-synuclein complex consequently increases cytotoxic protofibrils and covalent modification of functional enzymes. Thus, DA quinones play an important role in 'specific' DAergic neuro-degeneration of PD.

Ohlson CG, Hogstedt C. 1981 Dec. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury--a case-referent study. Scand J Work Environ Health 7(4):252-6.
Abstract: Parkinson's disease has been associated with heavy occupational exposure to carbon disulfide, and this solvent, as well as other organic solvents, may cause neurotoxic effects. Therefore, the hypothesis was raised that organic solvents in general may be associated with Parkinson's disease. A case-referent study design was applied, and some other suspected exposures were studied as well. The diagnosis registers of two Swedish hospitals were used as the source of subjects. Male in-patients with Parkinson's disease (the cases) or subarachnoid hemorrhage (referents), with symptom appearance between 35-69 a of age and residence in the vicinity of the hospitals, were included in the study. Occupational exposure to the chemicals under study were determined from questionnaire answers of 91 cases and 75 referents. No differences in exposure frequency to organic solvents in general were observed, but three cases had been exposed to carbon disulfide compared to none of the referents. Six cases, but only two referents, had been exposed to mercury, and further exploration of a possible association between exposure to mercury and Parkinson's disease is recommended. The outcome of the study does not support the hypothesis that occupational exposure to organic solvents in general increases the risk of Parkinson's disease, but the confidence intervals of the odds ratios do not rule out such possibilities.

Omar FA, Farag HH, Bodor N. 1994. Synthesis and evaluation of a redox chemical delivery system for brain-enhanced dopamine-containing an activated carbamate-type ester. J Drug Target 2(4):309-316.
Abstract: A chemical delivery system (CDS) for enhanced delivery of dopamine to brain tissue, based on a dihydropyridine double left right arrow pyridinium salt redox system, was modified to include an activated carbamate ester. The dihydronicotinate moiety was chemically attached to the amino group of dopamine (DA) by acylation with chloroethyl chloroformate, followed by condensation with sodium nicotinate under mild conditions. The product was selectively N-alkylated at the pyridine ring and subjected to regioselective reduction to the corresponding 1,4-dihydropyridine derivative, DA-CDSac. In vitro stability of the new compound was studied in phosphate buffers at mild acidic, physiological, and mild alkaline pH values. Oxidation studies showed facile conversion of the dihydronicotinate, DA-CDSac, is readily converted to the corresponding

quaternary salt, both chemically and enzymatically. In vivo studies in rats did not detect sustained increases in brain levels of the quaternary salt after i.v. dosing with DA-CDSac. However, the new CDS appeared to change spontaneous locomotor activity in rats after i.v. administration which may be due to altered central DA neuronal activity.

Ortegacesena J, Espinosatorres F, Lopezcarrillo L. 1994. Health risk control for organophosphate pesticides in mexico - prospects under the north-american-free-trade-agreement. Salud Publica Mex 36(6):624-632.
Abstract: This paper discusses recent trends concerning the commercialization of pesticides in Mexico and focuses on organophosphates and their potential health risk impact. It points out the existing lack of knowledge on health effects associated to chronic exposure to organophosphate pesticides. A need for both toxicological and epidemiologic studies of chronic exposure is identified. Regulatory programs for pesticides in Mexico and the United States are also compared. The paper also addresses the possibility of effective enforcement of environmental and health regulations in Mexico as a result of more rigorous surveillance under NAFTA.

Orth M, Tabrizi SJ, Schapira AHV, Cooper JM. 2003. alpha-Synuclein expression in HEK293 cells enhances the mitochondrial sensitivity to rotenone. Neurosci Lett 351(1):29-32.
Abstract: Mitochondrial dysfunction has been implicated in the aetiology of sporadic Parkinson's disease but its role in the disease mechanism is not clear. We have investigated the short term effect of G209A mutant or wild-type a-synuclein expression upon mitochondrial function using stable inducible cell models. Mitochondrial respiratory chain activities and membrane potential were normal suggesting that increased wild-type or mutant alpha-synuclein expression did not directly affect these parameters. However, both wild-type and mutant G209A alpha-synuclein expression enhanced the fall in mitochondrial membrane potential induced by the complex I inhibitor rotenone. This suggests an indirect interaction between alpha-synuclein expression and mitochondrial function which could render the mitochondria more vulnerable to inhibition by potential endogenous or exogenous factors found in dopaminergic neurones. (C) 2003 Elsevier Ireland Ltd. All rights reserved.

Orth M, Tabrizi SJ, Tomlinson C, Messmer K, Korlipara LVP, Scapira AHV, Cooper JM. 2004. G209A mutant alpha synuclein expression specifically enhances dopamine induced oxidative damage. Neurochem Int 45(5):669-676.
Abstract: Alpha synuclein protein may play an important role in familial and sporadic Parkinson's disease pathology. We have induced G209A mutant or wild-type alpha-synuclein expression in stable HEK293 cell models to determine if this influences markers of oxidative stress and damage under normal conditions or in the presence of dopamine or paraquat. Induced wild-type or mutant alpha-synuclein expression alone had no effect upon levels of oxidative stress or damage, as measured by glutathione levels or aconitase activity. Both wild-type and mutant alpha-synuclein expression decreased the oxidative damage induced by

paraquat, although the protection was less marked with mutant alpha-synuclein expression. This suggests that alpha-synuclein expression may either have anti-oxidant properties or may upregulate cellular antioxidant levels, a function that was diminished by the G209A mutation. However, mutant but not wild-type alpha-synuclein expression specifically enhanced dopamine associated oxidative damage. Non-expressing cells treated with reserpine to inhibit the vesicular monoamine compartmentalisation produced similar results. However, consistent with the hypothesis that mutant alpha-synuclein disrupts vesicular dopamine compartmentalization, this effect was diminished in cells expressing mutant alpha-synuclein. This may result in increased dopamine metabolism and cause selective oxidative damage to dopaminergic cells. (C) 2004 Elsevier Ltd. All rights reserved.

Ossowska K, Wardas J, Kuter K, Nowak P, Dabrowska J, Bortel A, Labus L, Kwiecinski A, Krygowska-Wajs A, Wolfarth S. 2005. Influence of paraquat on dopaminergic transporter in the rat brain. Pharmacological Reports 57 (3):330-335.
Abstract: Selective toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP), a parkinsonism inducing compound, is well known to be related to an uptake of its active metabolite MPP+ into dopaminergic neurons by dopamine transporter (DAT). The aim of the present study was to examine whether paraquat, a commonly used herbicide, which is-an 1-methyl-4-phenyl-pyridinium ion (MPP+) analogue, affects DAT in vivo in rats. Paraquat administered at a dose of 10 mg/kg ip decreased the binding of [H-3]GBR 12,935 to DAT measured by quantitative autoradiography in the dorsal and ventral caudate-putamen, but not in the substantia nigra pars compacta. Moreover, this compound increased the level of 3-methoxytyramine (3-MT) and 3-MT/dopamine ratio in the anterior and posterior caudate-putamen measured by HPLC with electrochemical detection. No other alterations in the levels of dopamine and its metabolites were found in the caudate-putamen and substantia nigra. The present study seems to suggest that systemic paraquat administration affects striatal DAT and dopamine metabolism in the nigrostriatal neurons in rats which may be crucial for its neurotoxic effects on dopaminergic neurons.

Ossowska K, Wardas J, Smialowska M, Kuter K, Lenda T, Wieronska JM, Zieba B, Nowak P, Dabrowska J, Bortel A, Kwiecinski A, Wolfarth S. 2005. A slowly developing dysfunction of dopaminergic nigrostriatal neurons induced by long-term paraquat administration in rats: an animal model of preclinical stages of Parkinson's disease? Eur J Neurosci 22(6):1294-1304.
Abstract: The aim of the present study was to examine the influence of the long-term paraquat administration on the dopaminergic nigrostriatal system in rats. Paraquat was injected at a dose of 10 mg/kg i.p. for 4-24 weeks. We found that this pesticide reduced the number of tyrosine hydroxylase-immunoreactive neurons of the substantia nigra; after the 4-week treatment the reduction (17%, nonsignificant) was confined to the rostrocentral region of this structure but, after 24 weeks, had spread along its whole length and was approximate to 37%. Moreover, it induced a

biphasic effect on dopaminergic transmission. First, levels of dopamine, its metabolites and turnover were elevated (4-8 weeks) in the caudate-putamen, then all these parameters returned to control values (12 weeks) and dropped by 25-30% after 24 weeks. The binding of [H-3]GBR 12,935 to dopamine transporter in the caudate-putamen was decreased after 4-8 weeks, then returned to control values after 12 weeks but was again decreased after 24 weeks. Twenty-four-week paraquat administration also decreased the level of tyrosine hydroxylase (Western blot) in the caudate-putamen. In addition, paraquat activated serotonin and noradrenaline transmission during the first 12 weeks of treatment but no decreases in levels of these neurotransmitters were observed after 24 weeks. The above results seem to suggest that long-term paraquat administration produces a slowly progressing degeneration of nigrostriatal neurons, leading to delayed deficits in dopaminergic transmission, which may resemble early, presymptomatic, stages of Parkinson's disease.

Packer MA, Miesel R, Murphy MP. 1996. Exposure to the parkinsonian neurotoxin 1-methyl-4-phenylpyridinium (MPP(+)) and nitric oxide simultaneously causes Cyclosporin A-sensitive mitochondrial calcium efflux and depolarisation. Biochem Pharmacol 51(3 ):267-273.
Abstract: The effect of the parkinsonian neurotoxin, 1-methyl-4-phenylpyridinium (MPP(+)) together with nitric oxide donors on mitochondrial calcium homeostasis and membrane potential was investigated. Simultaneous exposure of calcium-loaded mitochondria to MPP(+) and nitric oxide donors led to Cyclosporin A-sensitive mitochondrial calcium efflux and depolarisation. When MPP(+) was replaced with the respiratory inhibitor rotenone, mitochondrial calcium efflux and depolarisation also occurred. As both MPP(+) and rotenone induce mitochondrial superoxide formation, the possibility that calcium efflux and depolarisation were due to peroxynitrite formation from reaction of superoxide with nitric oxide was investigated. It was shown that simultaneous exposure of mitochondrial membranes to nitric oxide donors and rotenone led to peroxynitrite formation. The possible roles of nitric oxide, peroxynitrite, mitochondrial depolarisation, and calcium efflux in MPP(+) toxicity are discussed.

Pall ML. 2002. NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. FASEB J 16(11):1407-1417.
Abstract: Multiple chemical sensitivity (MCS) is a condition where previous exposure to hydrophobic organic solvents or pesticides appears to render people hypersensitive to a wide range of chemicals, including organic solvents. The hypersensitivity is often exquisite, with MCS individuals showing sensitivity that appears to be at least two orders of magnitude greater than that of normal individuals. This paper presents a plausible set of interacting mechanisms to explain such heightened sensitivity. It is based on two earlier theories of MCS: the elevated nitric oxide/peroxynitrite theory and the neural sensitization theory. It is also based on evidence implicating excessive NMDA activity in MCS. Four sensitization mechanisms are proposed to act synergistically, each based on known

physiological mechanisms: Nitric oxide-mediated stimulation of neurotransmitter (glutamate) release; peroxynitrite-mediated ATP depletion and consequent hypersensitivity of NMDA receptors; peroxynitrite-mediated increased permeability of the blood-brain barrier, producing increased accessibility of organic chemicals to the central nervous system; and nitric oxide inhibition of cytochrome P450 metabolism. Evidence for each of these mechanisms, which may also be involved in Parkinson's disease, is reviewed. These interacting mechanisms provide explanations for diverse aspects of MCS and a framework for hypothesis-driven MCS research.

Pan TH, Li XQ, Xie WJ, Jankovic J, Le W. 2005. Valproic acid-mediated Hsp70 induction and anti-apoptotic neuroprotection in SH-SY5Y cells. FEBS Lett 579(30):6716-6720.
Abstract: Valproic acid (VPA), an anticonvulsant and mood-stabilizing drug, has been reported to exert neuroprotection against a variety of insults. We now show that VPA attenuates rotenone (a potent complex I inhibitor)-induced apoptosis through the induction of heat shock protein 70, which may interact with apoptotic-protease-activating factor 1. Activation of p-Akt, p-Bcl-2, as well as p-Erk1/2 by VPA may be co-contributors to the protection. (c) 2005 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

Panov A, Dikalov S, Shalbueva N, Taylor G, Sherer T, Greenamyre T. 2004. Superoxide production and bioenergetic properties of rat brain and liver mitochondria in the Parkinson's disease induced by mitochondria toxin rotenone. Free Radic Biol Med 37:S158 .

Panov A, Dikalov S, Shalbuyeva N, Taylor G, Sherer T, Greenamyre T. 2005. Rotenone model of Parkinson disease - Multiple brain mitochondria dysfunctions after short term systemic rotenone intoxication. J Biol Chem 280(51):42026-42035.
Abstract: Chronic infusion of rotenone (Rot) to Lewis rats reproduces many features of Parkinson disease. Rot (3 mg/kg/day) was infused subcutaneously to male Lewis rats for 6 days using Alzet minipumps. Control rats received the vehicle only. Presence of 0.1% bovine serum albumin during the isolation procedure completely removed rotenone bound to the mitochondria. Therefore all functional changes observed were aftereffects of rotenone toxicity in vivo. In Rot rat brain mitochondria (Rot-RBM) there was a 30-40% inhibition of respiration in State 3 and State 3U with Complex I (Co-I) substrates and succinate. Rot did not affect the State 4 Delta Psi of RBM and rat liver mitochondria (RLM). However, Rot-RBM required two times less Ca2+ to initiate permeability transition (mPT). There was a 2-fold increase in O-2(-) or H2O2 generation in Rot-RBM oxidizing glutamate. Rot infusion affected RLM little. Our results show that in RBM, the major site of reactive oxygen species generation with glutamate or succinate is Co-I. We also found that Co-II generates substantial amounts of reactive oxygen species that increased 2-fold in the Rot-RBM. Our data suggest that the primary mechanism of the Rot toxic effect on RBM consists in a significant increase of O-2(-) generation that

causes damage to Co-I and Co-II, presumably at the level of 4Fe-4S clusters. Decreased respiratory activity diminishes resistance of RBM to Ca2+ and thus increases probability of mPT and apoptotic cell death. We suggest that the damage to Co-I and Co-II shifts O2. generation from the CoQ(10) sites to more proximal sites, such as flavines, and makes it independent of the RBM functional state.

Paolini M, Sapone A, Gonzalez FJ. 2004. Parkinson's disease, pesticides and individual vulnerability. Trends Pharmacol Sci 25(3):124-129.
Abstract: Current theories suggesting that degeneration of the nigrostriatal pathway following pesticide exposure could be a cause of Parkinson's disease (PD) are supported by epidemiological data linking environmental factors to an increased risk of parkinsonism. PD in humans is therefore thought to be a function of genetic predisposition, potentially associated with how efficiently an individual is able to metabolize dopamine-related neurotoxins. However, meta-analyses of susceptibility studies have failed to demonstrate clear-cut links between polymorphisms of xenobiotic-metabolizing enzymes (XMEs) and PD. We hypothesize that PD-related vulnerability to pesticides is linked to a strictly personal 'chemico-genetic XME blend' involving many variables. Innate XME genetic fingerprints undergo acquired 'modulations', which in turn are influenced by a myriad of individual exposures to chemical mixtures of environmental pollutants. We make a series of suggestions for the design of susceptibility studies focusing on persistent exposure to a specific pesticide in genetically defined population subsets of workers and gardeners within a geographically defined area.

Park J, Kim SY, Cha GH, Lee SB, Kim S, Chung J. 2005. Drosophila DJ-1 mutants show oxidative stress-sensitive locomotive dysfunction. Gene 361:133-139.
Abstract: DJ-1 is linked to an early-onset autosomal recessive Parkinson's disease (PD) characterized primarily by selective loss of dopaminergic (DA) neurons, which results in motor disturbances. However, our understanding on how mutations in DJ-I are related to PD is unclear. Here, we isolated the DJ-1 orthologue, DJ-1 beta, in Drosophila and characterized its expression and loss-of-function mutants. We observed its strongest expression in the adult stage of development and ubiquitous expression in the larval brain. Our homozygous mutants showed severe defects in locomotor ability without loss of DA neurons, consistent with the previous mice DJ-1 mutant studies ([Goldberg, M.S., Pisani, A., Haburcak, M., Vortherms, T.A., Kitada, T., Costa, C., Tong, Y., Martella, G., Tscherter, A., Martins, A., et al., 2005. Nigrostriatal dopaminergic deficits and hypokinesia caused by inactivation of the familial Parkinsonism-linked gene DJ-1. Neuron 45, 489-496.]; [Kiln, R.H., Smith, P.D., Aleyasin, H., Hayley, S., Mount, M.P., Pownall, S., Wakeham, A., You-Ten, A.J., Kalia, S.K., Home, P., Westaway, D., Lozano. A.M., Anisman, H., Park, D.S., Mak, T.W., 2005. Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and oxidative stress. Proc. Natl. Acad. Sci. USA 102, 5215-5220.]; [Chen, L., Cagniard, B., Mathews, T., Jones, S., Koh, H.C., Ding, Y., Carvey, P.M., Ling, Z., Kang, U.J., Zhuang, X., 2005. Age-dependent motor deficits and dopaminergic dysfunction in DJ-1 null mice. J. Biol. Chem. 280,

21418-21426.]). The locomotor activity of DJ-1 beta mutants was further decreased by paraquat-induced oxidative stress. Moreover, we found that Drosophila DJ-1 is prominently localized in mitochondria, suggesting that DJ-1 functions as a protector against oxidative stress in mitochondria. (c) 2005 Elsevier B. V. All rights reserved.

Park RM, Schulte PA, Bowman JD, Walker JT, Bondy SC, Yost MG, Touchstone JA, Dosemeci M. 2005. Potential occupational risks for neurodegenerative diseases. Am J Ind Med 48(1):63-77.
Abstract: Background Associations between occupations and neurodegenerative diseases (NDD) may be discernable in death certificate data. Methods Hypotheses generated from 1982 to 1991 study were tested in data from 22 states for the years 1992-1998. Specific occupations and exposures to pesticides, solvents, oxidative stressors, magnetic fields, and welding fumes were evaluated. Results About one third (26187) of the occupations hypothesized with neurodegenerative associations had statistically significant elevated mortality odds ratios (MOR)for the same outcome. Occupations with the largest MORs were (a) for presenile dementia (PSD)dentists, graders/sorters (non-agricultural), and clergy; (b) for Alzheimer's disease (AD)-bank tellers, clergy, aircraft mechanics, and hairdressers; (c) for Parkinson's disease (PD)-biological scientists, clergy, religious workers, and post-secondary teachers; and (d) for motor neuron disease (MND)-veterinarians, hairdressers, and graders and sorters (non-agricultural). Teachers had significantly, elevated MORs for all four diseases, and hairdressers for three of the four. Non -horticultural farmers below age 65 had elevated PD (MOR = 2.23, 95% CI = 1.47-3.26), PSD (MOR = 2.22, 95% CI = 1.10-4.05), and AD (MOR = 1.76, 95% CI = 1.04-2.81). Sixty hertz magnetic fields exhibited significant exposure-response for AD and, below age 65, for PD (MOR = 1.87, 95% CI=1.14-2.98) and MND (MOR=1.63, 95% CI=1.10-2.39). Welding had elevated PD mortality below age 65 (MOR = 1.77, 95% CI = 1.08-2.75). Conclusions Support was observed for hypothesized excess neurodegenerative disease associated with a variety, of occupations, 60 Hz magnetic fields and welding. Published 2005 Wiley-Liss, Inc.

Park SH, Choi WS, Yoon SY, Ahn YS, Oh YJ. 2004 Sep 24. Activation of NF-kappaB is involved in 6-hydroxydopamine-but not MPP+ -induced dopaminergic neuronal cell death: its potential role as a survival determinant. Biochem Biophys Res Commun 322(3):727-33.
Abstract: The nuclear factor-kappaB (NF-kappaB) family plays an important role in the control of the apoptotic response. Its activation has been demonstrated in both neurons and glial cells in many neurological disorders. In the present study, we specifically examined whether and to what extent NF-kappaB activation is involved in culture models of Parkinson's disease following exposure of MN9D dopaminergic neuronal cells to 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-4-phenylpyridinium ion (MPP(+)). Both analysis by immunocytochemistry and of immunoblots revealed that NF-kappaB-p65 was translocated into the nuclei following 6-OHDA but not MPP(+)-treatment. A time-dependent activation of NF-kappaB induced by 6-OHDA but not MPP(+) was also

demonstrated by an electrophoretic mobility shift assay. A competition assay indicated that not only NF-kappaB-p65 but also -p50 is involved in 6-OHDA-induced NF-kappaB activity. Co-treatment with an antioxidant, N-acetyl-l-cysteine, blocked 6-OHDA-induced activation of NF-kappaB signaling. In the presence of an NF-kappaB inhibitor, pyrrolidine dithiocarbamate (PDTC), 6-OHDA-induced cell death was accelerated while PDTC did not affect MPP(+)-induced cell death. Our data may point to a drug-specific activation of NF-kappaB as a survival determinant for dopaminergic neurons.

Pasha MK, Miyashita HK, Rajput AH. 2004. Accumulation of alanine in striatum of a rotenone rat model of Parkinson's disease. Mov Disord 19:S40.

Pasha MK, Sharma RK, Miyashita H, Rajput AH, Selvakumar P, Rajput AH. 2004. Increased N-myristoyltransferase activity in cardiac muscle of rotenone rat model of Parkinson's disease. Neurology 62(7):A10-A11.

Pasha MK, Sharma RK, Rajput AH. 2005. Increased myocardial N-myristoyltransferase activity in rotenone model of Parkinsonism. Int J Mol Med 15(6):987-991.
Abstract: There is widespread brain pathology in Parkinson's disease (PD), with the primary pathology in the substantia nigra. Oxidative stress is believed to play a role in cell death in PD. Rotenone is a mitochondrial toxin which call produce Parkinson syndrome (PS) in rats. Myristoyl-CoA:protein N-myristoyltransferase (NMT), which catalyzes the cotranslational transfer of myristate from myristoyl-CoA to the amino-terminal glycine residue of selected polypeptides, is increased in the myocardium of ischemia-reperfusion rat model myocardium. Animals received rotoneone (n=10) or placebo vehicle (n=6) via Alzet™ osmotic pumps. Mean cardiac muscle NMT activity of placebo treated (control) rats was 0.608 &PLUSMN; 0.366 units/mg protein. Rats with mild or no detectable PS foatures on rotenone showed slight (mean 0.853 &PLUSMN; 0.192) but insignificantly increased activity. Rats that had moderately severe PS features had higher level of NMT activity (mean 1.223 &PLUSMN; 0.057), which was borderline significant compared to controls (P=0.066). Rats with severe PS features had the highest NMT activity (1.353 &PLUSMN; 0.128) which was significantly greater compared to controls (P=0.003) and to the rats that had equivocal or no motor slowing (P=0.005). Our data show cardiac metabolic dysfunction in a rotenone rat model of PS. The severity of this change correlates with the severity of motor manifestations. Further studies of NMT activity in human PD cases and patients with cardiomyopathy of unknown cause may provide valuable information in these disorders.

Pavon N, Vidal L, Blanco L, Alvarez-Fonseca P, Torres-Montoya A, Lorigados L, Alvarez-Gonzalez L, Macias R. 1998. Factors which lead to death of neurones in neurodegenerative diseases. Rev Neurol 26(152):554-560.
Abstract: Objective. The objective of this paper was to review information related to the various factors which may trigger the mechanisms of cell death, induced or programmed, which take place in the nervous system

and their relationship with the aetiopathogenesis of the neurodegenerative diseases. Development, In recent years it has been recognized that cell death may he not only the consequence of accidental damage but also a sign of a suicide programme. This form of death is currently known as apoptosis. It is a process which is morphologically distinct from accidental cell death in necrosis. It does not cause ail inflammatory response. This type of death is not only involved in the development and haemostasis of tissues, but also in setting off neuronal degeneration in experimental models of Parkinson's disease, Huntington's chorea, etc. Conclusions, In the cell death occurring in neurodegenerative diseases there is more than one induction mechanism. Understanding the factors which trigger cell death, and the chain of events leading to this, gives grounds for the design of new pharmacological strategies for the treatment of these diseases.

Payami H, Zareparsi S. 1998. Genetic epidemiology of Parkinson's disease. J Geriatr Psychiatry Neurol 11(2):98-106.
Abstract: The cause of Parkinson's disease (PD) is unknown. The major risk factors identified to date are family history, age, and elements of rural living. Nearly one-third of all PD cases are familial, a small subset of which appears autosomal dominant; however, the majority exhibit no clear inheritance pattern. Autosomal dominant PD is genetically heterogeneous: two PD genes have been mapped to chromosomes 2 and 4 and there may be additional as yet unidentified genes. The common forms of PD-both familial and sporadic cases-appear to involve a complex interplay of genetic susceptibility and environmental exposure. The observations that rural residence and pesticide exposure increase the risk of developing PD, and that a synthetic drug, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, can cause parkinsonism, suggest that at least a subset of PD may be caused by a toxin. Furthermore, modest but significant associations have been reported between PD susceptibility and genes that regulate metabolism of drugs and neurotoxins. There is also evidence for mitochondrial dysfunction in PD, a finding that was recently traced to anomalies in mitochondrial DNA. At the present time, the genetics of PD appear to be complex, involving multiple nuclear genes and possibly mitochondrial genes as well.

Peng J, Mao XO, Stevenson FF, Hsu M, Andersen JK. 2004. The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway. J Biol Chem 279(31):32626-32632.
Abstract: Environmental exposure to the oxidant-producing herbicide paraquat has been implicated as a risk factor in Parkinson's disease. Although intraperitoneal paraquat injections in mice cause a selective loss of dopaminergic neurons in the substantia nigra pars compacta, the exact mechanism involved is still poorly understood. Our data show that paraquat induces the sequential phosphorylation of c-Jun N-terminal kinase (JNK) and c-Jun and the activation of caspase-3 and sequential neuronal death both in vitro and in vivo. These effects are diminished by the specific JNK inhibitor SP600125 and the antioxidant manganese(III) tetrakis (4-benzoic acid) porphyrin in vitro. Furthermore, JNK pathway inhibitor CEP-11004 effectively blocks paraquat-induced dopaminergic neuronal

death in vivo. These results suggest that the JNK signaling cascade is a direct activator of the paraquat-mediated nigral dopaminergic neuronal apoptotic machinery and provides a molecular linkage between oxidative stress and neuronal apoptosis.

Peng J, Stevenson FF, Doctrow SR, Andersen JK. 2005. Superoxide dismutase/catalase mimetics are neuroprotective against selective paraquat-mediated dopaminergic neuron death in the substantial nigra - Implications for Parkinson disease. J Biol Chem 280(32):29194-29198.
Abstract: Exposure of mice to the herbicide paraquat has been demonstrated to result in the selective loss of dopaminergic neurons of the substantia nigra, pars compacta (SNpc) akin to what is observed in Parkinson disease (PD). In this study, we investigate the efficacy of two synthetic superoxide dismutase/catalase mimetics (EUK-134 and EUK-189) in protecting against paraquat-induced dopaminergic cell death in both the rat dopaminergic cell line 1RB(3)AN(27) (N27) and primary mesencephalic cultures in vitro and in adult mice in vivo. Our data demonstrate that pretreatment with either EUK-134 or EUK-189 significantly attenuates paraquat-induced neurotoxicity in vitro in a concentration-dependent manner. Furthermore, systemic administration of EUK-189 decreases paraquat-mediated SNpc dopaminergic neuronal cell death in vivo. These findings support a role for oxidative stress in paraquat-induced neurotoxicity and suggest novel therapeutic approaches for neurodegenerative disorders associated with oxidative stress such as PD.

Peper M, Ertl M, Gerhard I. 1999. Long-term exposure to wood-preserving chemicals containing pentachlorophenol and lindane is related to neurobehavioral performance in women. Am J Ind Med 35( 6):632-641.
Abstract: Background The adverse neurobehavioral effects of long-term low exposure to wood-preserving chemicals (WPC) containing solvents, pentachlorophenol (PCP) and gamma-hexachlorocyclohexane (gamma-HCH; lindane), and other neurotoxicants were investigated in a neuropsychological group study. Methods Out of a population of 2,000 women visiting the outpatient practice of a gynecological department, a sample of 15 women aged 31-56 (mean 43) with long-term exposure to WPC verified by self-report, biological monitoring, and environmental samples was investigated Fifteen controls aged 42 (31-56) years were drawn from the same population and pair-wise matched with respect to sex, age, education, and estimated intelligence. Results For the exposed group, mean PCP serum level was 43.6 mu g/l and mean gamma-HCH blood level was 0.085 mu g/l. Mean duration of exposure was 10 (5-17) years. Intellectual functioning, attention, memory, and visuo-motor performance were examined suggesting significant group differences in visual short-term memory (Benton Test; d = 1.5, P =.005), verbal memory (paired associate learning and Peterson paradigm; d = 4.3 and 1.6 P <. 001), and an incidental learning task (d 2.3; P =.001). Frequent subjective complaints as assessed by questionnaire were attenuated motivation (d = 1.7; P =.001) increased fatigue (d = 1.6; P =.001), distractibility (d = 1.0; P =.003), and depressed mood (d = 1.9; P =.004). PCP blood level was significantly associated with paired-associate learning, Benton Test, and

reading/naming speed Conclusions Long-term low-dose exposure to WPC in the domestic environment could be related to subjective complaints (attention, mood and motivation) and to subtle alterations of neurobehavioral performance (e.g., working memory) in women Am. J. Ind. Med. 35:632-641, 1999. (C) 1999 Wiley-Liss, Inc.

Perez V, Moron J, Pasto M, Unzeta M. 2000. Neuroprotective aspects of a novel MAO-B inhibitor PF9601N. Neurobiology (Bp) 8(3-4):231-6.
Abstract: PF9601N is an acetylenic tryptamine derivative devoid of amphetamine-like properties, that behaves as suicide MAO-B inhibitor more potent than l-deprenyl. It is highly selective towards MAO-B and it neuroprotects from the neurotoxicity induced in C57Bl/6 adult mice by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). PF9601N also shows in vitro antioxidant properties by inhibiting the dopamine autoxidation. A potential therapeutic use in Parkinson's disease treatment is proposed for this compound.

Perier C, Bove J, Vila M, Przedborski S. 2003. The rotenone model of Parkinson's disease. Trends Neurosci 26(7):345-346.

Perry T, Lahiri DK, Chen DM, Zhou J, Shaw KTY, Egan JM, Greig NH. 2002. A novel neutrotrophic property of glucagon-like peptide 1: A promoter of nerve growth factor-mediated differentiation in PC12 cells. J Pharmacol Exp Ther 300(3):958-966.
Abstract: The insulinotropic hormone glucagon-like peptide-1 (7-36)-amide (GLP-1) has potent effects on glucose-dependent Insulin secretion, insulin gene expression, and pancreatic islet cell formation and is presently in clinical trials as a therapy for type 2 diabetes mellitus. We report on the effects of GLP-1 and two of its long-acting analogs, exendin-4 and exendin-4 WOT, on neuronal proliferation and differentiation, and on the metabolism of two neuronal proteins in the rat pheochromocytoma (PC12) cell line, which has been shown to express the GLP-1 receptor. We observed that GLP-1 and exendin-4 induced neurite outgrowth in a manner similar to nerve growth factor (NGF), which was reversed by coincubation with the selective GLP-1 receptor antagonist exendin (9-39). Furthermore, exendin-4 could promote NGF-initiated differentiation and may rescue degenerating cells after NGF-mediated withdrawal. These effects were induced in the absence of cellular dysfunction and toxicity as quantitatively measured by 3-(4,5-cimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide and lactate dehydrogenase assays, respectively. Our findings suggest that such peptides may be used in reversing or halting the neurodegenerative process observed in neurodegenerative diseases, such as the peripheral neuropathy associated with type 2 diabetes mellitus and Alzheimer's and Parkinson's diseases. Due to its novel twin action, GLP-1 and exendin-4 have therapeutic potential for the treatment of diabetic peripheral neuropathy and these central nervous system disorders.

Perry TL, Yong VW, Wall RA, Jones K. 1986 Sep 12. Paraquat and two endogenous analogues of the neurotoxic substance N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine do not damage dopaminergic

nigrostriatal neurons in the mouse. Neurosci Lett 69(3):285-9.
Abstract: C57 black mice were injected repeatedly with maximal tolerated doses of 4 different chemical analogues of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), or its metabolite N-methyl-4-phenylpyridinium ion (MPP+), in order to assess their possible neurotoxicity for dopaminergic nigrostriatal neurons and their potential for causing idiopathic Parkinson's disease. The 4 analogues were the herbicide paraquat, reduced paraquat (having two N-methyl-tetrahydropyridine moieties), N-methyl-1,2,3,4-tetrahydroisoquinoline, and 2-methyl-1,2,3,4-tetrahydro-beta-carboline, the latter two compounds being possible endogenous neurotoxins. Contents of striatal dopamine, measured by high-performance liquid chromatography with electrochemical detection one month after injections were completed, were not depleted by any of these 4 compounds in mice. They might conceivably prove more neurotoxic in primates.

Pesah Y, Pham T, Burgess H, Middlebrooks B, Verstreken P, Zhou Y, Harding M, Bellen H, Mardon G. 2004. Drosophila parkin mutants have decreased mass and cell size and increased sensitivity to oxygen radical stress. Development 131(9):2183-2194.
Abstract: Mutations in the gene parkin in humans (PARK2) are responsible for a large number of familial cases of autosomal-recessive Parkinson disease. We have isolated a Drosophila homolog of human PARK2 and characterized its expression and null phenotype. parkin null flies have 30% lower mass than wild-type controls which is in part accounted for by a reduced cell size and number. In addition, these flies are infertile, show significantly reduced longevity, and are unable to jump or fly. Rearing mutants on paraquat, which generates toxic free radicals in vivo, causes a further reduction in longevity. Furthermore, loss of parkin results in progressive degeneration of most indirect flight muscle (IFM) groups soon after eclosion, accompanied by apoptosis. However, parkin mutants have normal neuromuscular junction recordings during the third larval instar stage, suggesting that larval musculature is intact and that parkin is required only in pupal and adult muscle. parkin flies do not show an age-dependent dopaminergic neuron loss in the brain, even after aging adults for 3 weeks. Nevertheless, degeneration of IFMs demonstrates the importance or parkin in maintaining specific cell groups, perhaps those with a high-energy demand and the concomitant production of high levels of free radicals. parkin mutants will be a valuable model for future analysis of the mechanisms of cell and tissue degeneration.

Peters HA, Levine RL, Matthews CG, Chapman LJ. 1988 May. Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. Arch Neurol 45(5):537-40.
Abstract: Three groups of pesticide-exposed grain workers from three different work facilities experienced chronic central and peripheral nervous system dysfunction that appeared to be exposure related. The grain inspectors, malt laboratory workers, and grain elevator workers displayed higher prevalence rates of atypical parkinsonism, cerebellar signs, hearing loss, and sensory changes than would be expected in a nonneurologic control population. The 21 self-selected patients included in this report

exhibited cogwheel rigidity in 80% (17/21), decreased associated movements in 71% (15/21), distal sensory shading in 62% (13/21), intention tremulousness in 52% (11/21), resting tremulousness in 48% (10/21), and nerve conduction abnormalities in 44% (7/16). Carbon disulfide, a major component of the fumigant mixtures used, has been associated in the rayon industry, since the 1930s, with similar neurologic symptoms.

Peters HA, Levine RL, Matthews CG, Sauter S, Chapman L. 1986. Synergistic neurotoxicity of carbon tetrachloride/carbon disulfide (80/20 fumigants) and other pesticides in grain storage workers. Acta Pharmacol Toxicol (Copenh) 59 Suppl 7:535-46 .
Abstract: Neurophysiologic, neurobehavioral, and neuropsychologic profiles in 17 grain storage workers, 1 grain inspector, and 4 malting laboratory workers are described. The effects of CS2 toxicity as seen in viscose rayon workers as well as in experimental animals is remarkably similar to the clinical profile of our grain storage workers. CS2 use explains the dysfunction of peripheral axons, auditory nerve, the optic nerve, and the extrapyramidal system, as well as altered behavior and cognition changes. The signs and symptoms in these workers seem to be dose-related and we note that workers separated out from the areas where fumigation took place reported improvement not seen by fellow workers who continued the fumigant treatment routine. Likewise, malting laboratory workers exposed only to the grain dust from 3 to 7 years showed only minimal symptoms. Though a number of mechanism have been suggested for the alteration of neuropsychological function, the chelating ability of DDC derived from CS2 and its ability to markedly increase copper and zinc within the central nervous system suggests a mechanism of toxicity analogous to copper intoxication as in Wilson's Disease and may explain the production of extrapyramidal symptoms in these patients. Chelation of copper might prove therapeutic in CS2 poisoning. It is obvious that both basic and clinical research will be necessary to sort out the questions raised. We applaud the EPA's decision to ban the use of 80/20 fumigants and also methyl bromide, and trust that similar toxic substances be carefully studied before their selection for replacing these previous toxic agents. We further decry the technique of re-introducing grain dust into the food chain rather than destroying it, since the dust contains very high residues of fumigant material. We speculate on the possible role of CS2 and other pesticides in the food chain and the incidence of Parkinsonian symptoms in these patients and the general public.

Petkova V. 2001. [Diagnostic problems of post-intoxication states]. Med Tr Prom Ekol (4):21-4.
Abstract: Complete clinical examination covered 37 patients in various stages after acute occupational poisonings with pesticides (8 examinees), with explosive gases (9 subjects), with carbon oxide (3 examinees), with cadmium oxides (1 examinee), with nitrogen compounds (4 ones), with sulfurous gases (2 examinees), with organic solvents (10 subjects) including chlorinated hydrocarbons (2 subjects). Post-intoxication period appeared to include syndromes characteristic for each poison and

corresponding to severity of acute state (from cephalgia to parkinsonism and thyrotoxicosis after acute poisoning with carbon oxide, organic neurologic signs and toxic hepatitis after acute poisoning with phosphorus organic compounds, cerebral asthenia after acute exposure to organic solvents, severe encephalopathy and toxic auditory and optic neuropathy after hydrogen sulfide). Inadequate medical rehabilitation and continuous occupational exposure induced deterioration in clinical signs and advanced post-intoxication syndromes.

Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, Masaki KH, Blanchette PL, Popper JS, Foley D, Launer L, White LR. 2002. Plantation work and risk of Parkinson disease in a population-based longitudinal study. Arch Neurol 59(11):1787-1792.
Abstract: Context: Parkinson disease (PD) has an unknown cause; however, convincing evidence is emerging that indicates pesticides can selectively injure the dopaminergic system in laboratory animals. Retrospective studies in humans demonstrate a link between exposure to agricultural lifestyle factors and PD. Objective: To determine whether working on a plantation in Hawaii and exposure to pesticides are associated with an increased risk of PD decades later. Design and Setting: Prospective cohort study based on the island of Oahu, Hawaii, with 30 years of follow-up. Years of work on a plantation were assessed by questionnaire at study enrollment in 1965. Self-reported information on pesticide exposure was collected at a separate examination 6 years later. Participants: Participants were 7986 Japanese American men born between 1900 and 1919 who were enrolled in the longitudinal Honolulu Heart Program. Main Outcome Measures: Incident PD was determined by medical record review or by an examination conducted by a study neurologist at a later date.. Results: During follow-up, 116 men developed PD. Age-adjusted incidence increased significantly among men who worked more than 10 years on a plantation. The relative risk of PD was 1.0 (95% confidence interval, 0.6-1.6), 1.7 (95% confidence interval, 0.8-3.7), and 1.9 (95% confidence interval, 1.0-3.5) for men who worked on a plantation 1 to 10 years, 11 to 20 years, and more than 20 years compared with men who never did plantation work (P=.006, test for trend). Age-adjusted incidence of PD was higher in men exposed to pesticides than in men not exposed to pesticides although this was not statistically significant (P=.10, test for trend). Conclusion: These longitudinal observations regarding plantation work in Hawaii support case-control studies suggesting that exposure to pesticides increases the risk of PD.

Phillips H. 2004. Pesticide link to Parkinson's grows stronger. New Scientist 184 (2472):18.

Pittman JT, Dodd CA, Klein BG. 2003. Immunohistochemical changes in the mouse striatum induced by the pyrethroid insecticide permethrin. International Journal of Toxicology 22(5):359-370.
Abstract: Epidemiological studies have linked insecticide exposure and Parkinson's disease. In addition, some insecticides produce damage or physiological disruption within the dopaminergic nigrostriatal pathway of

non-humans. This study employed immunohistochemical analysis in striatum of the C57BL/6 mouse to clarify tissue changes suggested by previous pharmacological studies of the pyrethroid insecticide permethrin. Dopamine transporter, tyrosine hydroxylase, and glial fibrillary acidic protein immunoreactivities were examined in caudate-putamen to distinguish changes in amount of dopamine transporter immunoreactive protein from degeneration or other damage to dopaminergic neuropil. Weight-matched pairs of pesticide-treated and vehicle-control mice were dosed and sacrificed on the same days. Permethrin at 0.8, 1.5 and 3.0 mg/kg were the low doses and at 200 mg/kg the high dose. Brains from matched pairs of mice were processed on the same slides using the avidin-biotin technique. Four fields were morphometrically located in each of the serial sections of caudate-putamen, digitally photographed, and immunopositive image pixels were counted and compared between members of matched pairs of permethrin-treated and vehicle-control mice. For lowdoses, only 3.0 mg/kg produced a significant decrease in dopamine transporter immunostaining. The high dose of permethrin did not produce a significant change in dopamine transporter or tyrosine hydroxylase immunostaining, but resulted in a significant increase in glial fibrillary acidic protein immunostaining. These data suggest that a low dose of permethrin can reduce the amount of dopamine transporter immunoreactive protein in the caudate-putamen. They also suggest that previously reported reductions in dopamine uptake of striatal synaptosomes of high-dose mice may be due to nondegenerative tissue damage within this region as opposed to reductions of dopamine transporter protein or death of nigrostriatal terminals. These data provide further evidence that insecticides can affect the primary neurodegenerative substrate of Parkinson's disease.

Pond SM. 1996. Illumination of therapeutics by toxicology: A personal view. Clin Exp Pharmacol Physiol 23(10-11):1010-1013.
Abstract: 1. My specialties are therapeutics and toxicology. When we think in classical terms about drugs, therapeutics refers to curative healing, toxicology to the capacity to produce harm. However, they are not opposite disciplines, but rather reflect a continuum along the dose-response curve of a drug or toxin. Since antiquity, the study of toxicology has underpinned and illuminated therapeutics. Even the most potent toxins, such as botulinum and ricin, are used for therapeutic purposes. 2. In the case of one of my favourite research topics, the herbicide paraquat, I illustrate how investigating methods to treat patients poisoned by it has led to important advances in knowledge in medicine and therapeutics. Studying paraquat has launched my own research group on a path towards elucidating the mechanisms of the chronic neurological side effects of the antipsychotic drug, haloperidol, which is used widely to treat schizophrenia. In tracing these tortuous paths, the roles that serendipity and creativity play in research and their implications far education and funding policies are highlighted.

Prasad KN, Cole WC, Kumar B. 1999. Multiple antioxidants in the prevention and treatment of Parkinson's disease. J Am Coll Nutr 18 (5):413-423.

Abstract: Parkinson's disease (PD) is one of the major progressive neurological disorders for which no preventative or long-term effective treatment strategies are available. Epidemiologic studies have failed to identify specific environmental, dietary or lifestyle risk factors for PD except for toxic exposure to manganese, meperidine (Demerol(R), the "designer drug" version of which often contains a toxic byproduct of the synthesis, 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine [MPTP]), and some herbicides and pesticides. The search for genetic risk factors such as mutation, overexpression or underexpression of nuclear penes in DA neurons in idiopathic PD has not been successful as yet Polymorphism in certain genes appears to be a risk factor, but there is no direct evidence for the causal relationship between polymorphism and increased risk of PD. In familial PD. mutation in the alpha-synuclein gene is associated with the disease, but a direct role of this gene in degeneration of DA neurons remains to be established. Although mutations in the Parkin gene has been associated with autosomal recessive juvenile Parkinson's disease, the role of this gene mutation in causing degeneration of DA neurons has not been defined. We have reported that in hereditary PD, a mutation in the alpha-synuclein gene may increase the sensitivity of DA neurons to neurotoxins. We hypothesize that, in idiopathic PD, epigenetic (mitochondria, membranes, protein modifications) rather than genetic events are primary targets which, when impaired, initiate degeneration in DA neurons, eventually leading to cell death. Although the nature of neurotoxins that cause degeneration in DA neurons in PD is not well understood, oxidative stress is one of the intermediary risk factors that could initiate and/or promote degeneration of DA neurons. Therefore, supplementation with antioxidants may prevent or reduce the rate of progression of this disease. Supplementation with multiple antioxidants at appropriate doses is essential because various types of free radicals are produced, antioxidants vary in their ability to quench different free radicals and cellular environments vary with respect to their lipid and aqueous phases. L-dihydroxyphenylalanine (L-dopa) is one of the agents used in me treatment of PD. Since L-dopa is known to produce free radicals during its normal metabolism, the combination of L-dopa with high levels of multiple antioxidants may improve the efficacy of L-dopa therapy.

Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. 2001. Environmental risk factors and Parkinson's disease: A metaanalysis. Environ Res 86(2): 122-127.

Abstract: The study aim was to examine the association between Parkinson's disease (PD) and exposure to environmental factors such as living in a rural area, well water use, farming, exposure to farm animals, or living on a farm, and pesticides. A series of metaanalyses of peer-reviewed studies were performed, using 16 studies for living in rural area, 18 studies for well water drinking, 11 studies for farming, and 14 studies for pesticides. Prior to the metaanalyses, all studies were reviewed and evaluated for heterogeneity and publication bias. Significant heterogeneity among studies was detected and combined odds ratio (OR) was calculated using the random and the fixed-effect models. The majority of the studies

reported consistent elevation in the risk of PD with exposure to environmental factors such as rural living and farming. The combined OR for rural residence was 1.56 [95% confidence interval (95% CI) 1.18-2.07] for all the studies, and 2.17(95% CI 1.54-3.06) for studies performed in United States. The combined OR for well water use was 1.26 (95% CI 0.97-1.64) for all the studies, and 1.44(95% CI 0.92-2.24) for studies done in United States. The combined OR for farming, exposure to farm animals, or living on a farm was 1.42 (95% CI 1.05-1.91) for all studies, and 1.72 (95% CI 1.20-2.46) for studies done in United States. The combined OR for pesticides exposure was 1.85(95% CI 1.31-2.60) for all studies, and 2.16 (95% CI 1.95-2.39) for studies done in United States. Dose-response relationships could not be established due to the imprecise nature of the reported data. Our findings suggest that living in a rural area, drinking well water, farming, and exposure to pesticides may be a risk factor for developing PD. (C) 2001 Academic Press.

Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. 2000. A meta-analysis of Parkinson's disease and exposure to pesticides. Neurotoxicology 21(4): 435-440.
Abstract: This study examined the association between Parkinson's disease (PD) and exposure to pesticides. A series of meta-analysis of peer-reviewed studies were performed using 19 studies published between 1989 and 1999. Prior to the meta-analysis, all studies were reviewed and evaluated for heterogeneity and publication bias. Significant heterogeneity among studies was detected and combined odds ratio (OR) was calculated using the random effect model. The majority of the studies reported consistent elevation in the risk of PD with exposure to pesticides. The combined OR studies was 1.94 [95% confidence interval (95% CI) 1.49-2.53] for all the studies, and 2.15 (95% CI 1.14-4.05) for studies performed in United States. Although the risk of PD increased with increased duration of exposure to pesticides, no significant dose-response relation was established, and no specific type of pesticide was identified Our findings suggest that exposure to pesticides may be a significant risk factor for developing PD. (C) 2000 Inter Press, Inc.

Przedborski S, Ischiropoulos H. 2005. Reactive oxygen and nitrogen species: Weapons of neuronal destruction in models of Parkinson's disease. Antioxidants & Redox Signaling 7(5-6):685-693.
Abstract: Parkinson's disease (PD) is a common neurodegenerative disease whose etiology and pathogenesis remain mainly unknown. To investigate its cause and, more particularly, its mechanism of neuronal death, numerous in vivo experimental models have been developed. Currently, both genetic and toxic models of PD are available, but the use of neurotoxins such as 6-hydroxydopamine, paraquat, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, and rotenone are still the most popular means for modeling the destruction of the nigrostriatal dopaminergic neurons seen in PD. These four neurotoxins, although distinct in their intimate cytotoxic mechanisms, kill dopaminergic neurons via a cascade of deleterious events that consistently involves oxidative stress. Herein, we review and compare the molecular mechanisms of 6-hydroxydopamine,

paraquat, 1-methyl-4-phenyl-1,2,3,6tetrahydropyridine, and rotenone, placing the emphasis of our discussion on how reactive oxygen and nitrogen species contribute to the neurotoxic properties of these four molecules. As the reader will discover, to achieve the above stated goal, we had to not only appraise recent findings, but also revisit earlier landmark studies to provide a comprehensive view on this topic. This approach also enabled us to describe how our understanding of the mechanism of actions of certain toxins has evolved over time, which is particularly striking in the case of the quatrogenarian neurotoxin, 6-hydroxydopamine.

Przuntek H, Muller T. 1999. Clinical efficacy of budipine in Parkinson's disease. Journal of Neural Transmission-Supplement (56):75-82.
Abstract: The lipophilic t-butyl analog of 1-alkyl-4,4-diphenyl piperidine, budipine, possesses a polyvalent spectrum of mechanisms of action. Budipine experimentally increased the brain content of norepinephrine, serotonine, dopamine and histamine in reserpine treated rats. Budipine did not alter the receptor affinity of these neurotransmitters but antagonizes the effect of NMDA at its receptor binding site in vitro. Budipine reduced MPP+ toxicity in the nigrostriatal system of mice. This complex pharmacologic profile is not comparable to the one of convenient antiparkinsonian drugs. In clinical trials budipine reduced tremor, akinesia and rigidity. Budipine induced a relevant additional positve effect in patients with an optimal dopaminergic therapy based on levodopa and dopamine agonists, such as bromocriptine. Current available data suggest that the need for levodopa application in early stages of the disease may be postponed by budipine and that the long-term application of budipine may induce a levodopa-sparing effect.

Purkerson-Parker S, Mcdaniel KL, Moser VC. 2001. Dopamine transporter binding in the rat striatum is increased by gestational, perinatal, and adolescent exposure to heptachlor. Toxicol Sci 64(2):216-223.
Abstract: Heptachlor is a persistent cyclodiene pesticide that affects GABAergic function. Recent reports indicate that heptachlor exposure also alters dopamine transporter (DAT) expression and function in adult mice. The aim of this study was to determine whether gestational, perinatal, and/or adolescent heptachlor exposure in rats altered dopamine-receptor and DAT binding. Adolescent exposure to dieldrin was included to evaluate the generality of the findings. Sprague-Dawley rats received doses (po) ranging from 0 to 8.4 mg/kg/day of heptachlor, or dieldrin, 3 mg/kg/day, during different developmental periods. There were dose-related decreases in maternal weight gain and pup survival, as well as delayed righting reflex, at heptachlor doses greater than or equal to3 mg/kg/day. There were no changes in striatal dopamine receptor-D1 ([H-3]SCH-23390) and -D2 ([H-3]spiperone) binding in preweanling pups exposed perinatally to heptachlor, and no differences in the response of adult rats to the motor activity-increasing effects of d-amphetamine. However, there were significant (27-64%) increases in striatal DAT binding of [H-3]mazindol in preweanling rats exposed only gestationally. In rats exposed perinatally and/or during adolescence, there were also increases (34-65%) in striatal

DAT binding at postnatal days (PND) 22, 43, and 128. Adolescent exposure to dieldrin also increased DAT binding. In other rats exposed perinatally and throughout adolescence, even the lowest dose of heptachlor 0.3 mg/kg/d increased DAT binding on PND 130. The DAT affinity for mazindol was unchanged in heptachlor-exposed striata. In vitro binding studies indicated that heptachlor (greater than or equal to 10 muM) displaced mazindol binding. Thus, gestational, perinatal, and/or adolescent exposure to heptachlor produced an increase in DAT binding as early as PND 10, and this change persisted into adulthood.

Quigley PM, Korotkov K, Baneyx F, Hol WGJ. 2004. A new native EcHsp31 structure suggests a key role of structural flexibility for chaperone function. Protein Sci 13(1):269-277.
Abstract: Heat shock proteins and proteases play a crucial role in cell survival under conditions of environmental stress. The heat shock protein Hsp31, produced by gene hchA at elevated temperatures in Escherichia coli, is a homodimeric protein consisting of a large A domain and a smaller P domain connected by a linker. Two catalytic triads are present per dimer, with the Cys and His contributed by the A domain and an Asp by the P domain. A new crystal Form II confirms the dimer and catalytic triad arrangement seen in the earlier crystal Form I. In addition, several loops exhibit increased flexibility compared to the previous Hsp31 dimer structure. In particular, loops D2 and D3 are intriguing because their mobility leads to the exposure of a sizable hydrophobic patch made up by surface areas of both subunits near the dimer interface. The residues creating this hydrophobic surface are completely conserved in the Hsp31 family. At the same time, access to the catalytic triad is increased. These observations lead to the hypothesis for the functioning of Hsp31 wherein loops D2 and D3 play a key role: first, at elevated temperatures, by becoming mobile and uncovering a large hydrophobic area that helps in binding to client proteins, and second, by removing the client protein from the hydrophobic patch when the temperature decreases and the loops adopt their low-temperature positions at the Hsp31 surface. The proposed mode of action of flexible loops in the functioning of Hsp31 may be a general principle employed by other chaperones.

Rachinger J, Fellner FA, Stieglbauer K, Trenkler J. 2002 Sep. MR changes after acute cyanide intoxication. AJNR Am J Neuroradiol 23(8):1398-401.
Abstract: We describe MR changes that occurred 3 and 6 weeks after a suicide attempt with cyanide. The toxicity of cyanide causes damage, primarily to the basal ganglia, and those changes were visible as altered signal intensity on the first MR images. Extensive areas of hemorrhagic necrosis were seen 6 weeks later. Our case shows pseudolaminar necrosis along the central cerebral cortex 3 weeks after cyanide poisoning, showing that the sensorimotor cortex is also a site for toxic necrosis because of its high oxygen dependency.

Raft D, Newman M, Spencer R. 1972 Mar. Suicide on L-dopa. South Med J 65(3): 312 passim.

Ragnarsdottir KV. 2000. Environmental fate and toxicology of organophosphate pesticides. Journal of the Geological Society 157:859-876.
Abstract: Organophosphate pesticides (OPs) are generally regarded as safe for use on crops and animals due to their relatively fast degradation rates. Their degradation varies as a function of microbial composition, pH, temperature, and availability of sunlight. Under laboratory conditions (25 degrees C and pH 7) biodegradation is about one order of magnitude faster than chemical hydrolysis, which in turn is roughly ten times faster than photolysis. Microbial biomass often needs a lengthy adaptation period in which soil bacteria mutate to be able to metabolize OPs. Biodegradation is thus in general an order of magnitude faster in soils that have had repeated applications of OPs compared to control soils which have never had OP applications. Because OPs are relatively soluble, they often enter surface and groundwaters. In the latter OPs are primarily broken down through chemical hydrolysis, which is pH dependent. Hydrolysis half-life of an OP pesticide of 10 days in the laboratory increases to one year if the pH of the water is 6 and the temperature 5 degrees C, suggesting that OPs can persist in the environment for long periods of time. Indeed, OPs are detected in soils years after application. Why this environmental persistence occurs is not clear, but it may be due to sorption of the OPs to soil particles, making them unavailable for microbial metabolism. Example calculations and literature data show that conditions can occur in soil where OPs are preserved and transferred to humans through food. A review of the literature shows that OPs are highly toxic and that human exposure is undesirable. Evidence suggests that OPs are mutagenic and teratogenic and that a large number of modem-day diseases of the nervous and immune system of mammals can be linked to these pesticides. These include BSE (mad cows disease), CJD, Gulf War syndrome, Parkinson's disease and multiple sclerosis, arguing for a thorough examination of the environmental fate and toxicology of OPs as well as their use.

Rainey JM Jr. 1977 Apr. Disulfiram toxicity and carbon disulfide poisoning. Am J Psychiatry 134(4):371-8.
Abstract: The author compared the neurotoxic effects of disulfiram with those of carbon disulfide, a disulfiram metabolite. The results suggest that carbon disulfide is responsible for the behavioral and neurological side effects of disulfiram. If this is so, then some other toxic effects of carbon disulfide, including parkinsonism, choreoathetosis, and thalamic syndrome may follow the ingestion of more than 5 g of disulfiram by adults, and individuals receiving as little as 125 mg of disulfiram per day may be at a three- to four-fold greater risk for arteriosclerotic cardiovascular disease than a comparable population not receiving the drug.

Rajput AH, Uitti RJ. 1987. Paraquat and parkinsons-disease. Neurology 37(11): 1820-1821.

Rajput AH, Uitti RJ, Stern W, Laverty W, Odonnell K, Odonnell D, Yuen WK, Dua A. 1987. Geography, drinking-water chemistry, pesticides and herbicides and the etiology of parkinsons-disease. Can J Neurol Sci 14(3):414-418.

Ramsay RR, Krueger MJ, Youngster SK, Gluck MR, Casida JE, Singer TP. 1991. Interaction of 1-methyl-4-phenylpyridinium ion (mpp+) and its analogs with the rotenone piericidin binding-site of nadh dehydrogenase. J Neurochem 56(4):1184-1190.
Abstract: Nigrostriatal cell death in 1-methyl-4-phenyl-1,2,3,6-tetrahydropydropyridine (MPTP)-induced Parkinson's disease results from the inhibition of mitochondrial respiration by 1-methyl-4-phenylpyridinium (MPP+). MPP+ blocks electron flow from NADH dehydrogenase to coenzyme Q at or near the same site as do rotenone and piericidin and protects against binding of and loss of activity due to these inhibitors. The 4'-analogs of MPP+ showed increasing affinity for the site with increasing length of alkyl chain, with the lowest K(i), for 4'-heptyl-MPP+, being 6-mu-M. The 4'-analogs compete with rotenone for the binding site in a concentration-dependent manner. They protect the activity of the enzyme from inhibition by piericidin in parallel to preventing its binding, indicating that the analogs and piericidin bind at the same inhibitory site(s). The optimum protection, however, was afforded by 4'-propyl-MPP+. The lesser protection by the more lipophilic MPP+ analogs with longer alkyl chains may involve a different orientation in the hydrophobic cleft, allowing rotenone and piericidin to still bind even when the pyridinium cation is in a position to interrupt electron flow from NADH to coenzyme Q.

Ramsay RR, Singer TP. 1992. Relation of superoxide generation and lipid-peroxidation to the inhibition of nadh-q oxidoreductase by rotenone, piericidin-a, and mpp(+). Biochem Biophys Res Commun 189(1):47-52.

Rati ZPM, Yang H. 2004. The influence of rotenone for a-synuclein protein of SH-SY5Y cells. J Neurochem 88:54.

Reeves R, Thiruchelvam M, Baggs RB, Cory-Slechta DA. 2003. Interactions of paraquat and triadimefon: Behavioral and neurochemical effects. Neurotoxicology 24(6):839-850.
Abstract: Triadimefon (TDF), a triazole fungicide, and paraquat (PQ), a non-selective herbicide/dessicant, are both known to adversely impact brain dopaminergic function and are used in overlapping geographical areas of the US. Since real world situations indicate humans are exposed to a diverse mixture of chemicals, this study hypothesized that combined exposures to PQ + TDF could produce interactive effects by simultaneously attacking multiple target sites of dopamine systems. Thus, 10 mg/kg PQ (PQ10) and 25 or 50 mg/kg TDF(TDF25 and 50, respectively) were administered i.p. to male C57BL/6 mice, 2 per week for 12 weeks, either alone or in combination. Acutely, TDF50 increased horizontal and vertical activity with increased vertical activity still occurring 24 h later, indicative of sustained behavioral sensitization. Acutely, PQ decreased horizontal but not vertical activity with a lack of residual effects at 24 h. PQ prevented the increased levels of activity associated with TDF50. These interactions differed for horizontal and vertical activity, indicating their differential neurochemical mediation, and suggesting that they did not arise from simple additivity of PQ and TDF effects. Nor could the interactive effects be readily ascribed to corresponding neurochemical interactions, since all

treatments generally increased levels of DA and metabolites acutely in striatum and were associated with general reductions in levels of DA and metabolites and turnover in striatum and frontal cortex 7 days after the final treatment. Thus, TDF and PQ both separately and through interactions may serve as environmental risk factors through different mechanisms for dopaminergically-mediated behavioral dysfunctions. (C) 2003 Elsevier Science Inc. All rights reserved.

Reiter RJ. 1997. Aging and oxygen toxicity: Relation to changes in melatonin. Age 20(4):201-213.
Abstract: Melatonin (N-acetyl-5-methoxytryptamine) is a chemical mediator produced in the pineal gland and other sites in the body. The melatonin found in the blood is derived almost exclusively from the pineal gland. Since the pineal synthesizes melatonin primarily at night, blood levels of the indole are also higher at night (5-15 fold) than during the day. Some individuals on a nightly basis produce twice as much melatonin as others of the same age. Throughout life, the melatonin rhythm gradually wanes such that, in advanced age, melatonin production is usually at a minimum. Melatonin was recently found to be a free radical scavenger and antioxidant. It has been shown, in the experimental setting, to protect against both free radical induced DNA damage and oxidative stress-mediated lipid peroxidation. Pharmacologically, melatonin has been shown to reduce oxidative damage caused by such toxins as the chemical carcinogen safrole, carbon tetrachloride, paraquat, bacterial lipopolysaccharide, kainic acid, delta-aminolevulinic and amyloid beta peptide of Alzheimer's disease as well as a model of Parkinson's disease involving the drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Additionally, the oxidative damage caused by agents such as ionizing radiation and excessive exercise is reduced by melatonin. Since free radical-induced molecular injury may play a significant role in aging, melatonin's ability to protect against it suggests a potential function of melatonin in deferring aging and age-related, free radical-based diseases. Besides its ability to abate oxidative damage, other beneficial features of melatonin may be important in combating the signs of aging; these include melatonin's immune-stimulating function, its sleep-promoting ability, its function as an anti-viral agent, and general protective actions at the cellular level. Definitive tests of the specific functions of physiological levels of melatonin in processes of aging are currently being conducted.

Reiter RJ, Carneiro RC, Oh CS. 1997. Melatonin in relation to cellular antioxidative defense mechanisms. Horm Metab Res 29(8):363-372.
Abstract: Melatonin's actions in organisms are more widespread than originally envisaged. Over three decades ago, the changing pattern of nocturnal melatonin production was found to be the signal for the annual cycle of reproduction in photoperiodic species. Since then, melatonin's actions also have been linked to circadian rhythms, immune function, sleep, retinal physiology and endocrine functions in general. In recent years, however, the sphere of influence of melatonin was further expanded when the indole was found to be an effective free radical scavenger and antioxidant. Free radicals are toxic molecules, many being derived from

oxygen, which are persistently produced and incessantly attack and damage molecules within cells; most frequently this damage is measured as peroxidized lipid products, carbonyl proteins, and DNA breakage or fragmentation. Collectively, the process of free radical damage to molecules is referred to as oxidative stress. Melatonin reduces oxidative stress by several means. Thus, the indole is an effective scavenger of both the highly toxic hydroxyl radical, produced by the 3 electron reduction of oxygen, and the peroxyl radical, which is generated during the oxidation of unsaturated lipids and which is sufficiently toxic to propagate lipid peroxidation. Additionally, melatonin may stimulate some important antioxidative enzymes, i.e., superoxide dismutase, glutathione peroxidase and glutathione reductase. In in vivo tests, melatonin in pharmacological doses has been found effective in reducing macromolecular damage that is a consequence of a variety of toxic agents, xenobiotics and experimental paradigms which induce free radical generation. In these studies, melatonin was found to significantly inhibit oxidative damage that is a consequence of paraquat toxicity, potassium cyanide administration, lipopolysaccharide treatment, kainic acid injection, carcinogen administration, carbon tetrachloride poisoning, etc., as well as reducing the oxidation of macromolecules that occurs during strenuous exercise or ischemia-reperfusion. In experimental models which are used to study neurodegenerative changes associated with Alzheimer's and Parkinson disease, melatonin was found to be effective in reducing neuronal damage. Its lack of toxicity and the ease with which melatonin crosses morphophysiological barriers and enters subcellular compartments are essential features of this antioxidant. Thus far, most frequently pharmacological levels of melatonin have been used to combat oxygen toxicity. The role of physiological levels of melatonin, which are known to decrease with age, is being investigated as to their importance in the total antioxidative defense capacity of the organism.

Ren Y, Liu WH, Jiang HB, Jiang Q, Feng J. 2005. Selective vulnerability of dopaminergic neurons to microtubule depolymerization. J Biol Chem 280 (40):34105-34112.
Abstract: Parkinson disease (PD) is characterized by the specific degeneration of dopaminergic (DA) neurons in substantia nigra and has been linked to a variety of environmental and genetic factors. Rotenone, an environmental PD toxin, exhibited much greater toxicity to DA neurons in midbrain neuronal cultures than to non-DA neurons. The effect was significantly decreased by the microtubule-stabilizing drug taxol and mimicked by microtubule-depolymerizing agents such as colchicine or nocodazole. Microtubule depolymerization disrupted vesicular transport along microtubules and caused the accumulation of dopamine vesicles in the soma. This led to increased oxidative stress due to oxidation of cytosolic dopamine leaked from vesicles. Inhibition of dopamine metabolism significantly reduced rotenone toxicity. Thus, our results suggest that microtubule depolymerization induced by PD toxins such as rotenone plays a key role in the selective death of dopaminergic neurons.

Ren Y, Zhao JH, Feng J. 2003. Parkin binds to alpha/beta tubulin and increases

their ubiquitination and degradation. J Neurosci 23(8):3316-3324.
Abstract: In addition to inhibiting the mitochondrial respiratory chain, toxins known to cause Parkinson's disease (PD), such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and rotenone, also strongly depolymerize microtubules and increase tubulin degradation. Microtubules are polymers of tubulin alpha/beta heterodimers, whose correct folding requires coordinated actions of cellular chaperonins and cofactors. Misfolded tubulin monomers are highly toxic and quickly degraded through a hitherto unknown mechanism. Here we report that parkin, a protein-ubiquitin E3 ligase linked to PD, was tightly bound to microtubules in taxol-mediated microtubule coassembly assays. In lysates from the rat brain or transfected human embryonic kidney (HEK) 293 cells, alpha-tubulin and beta-tubulin were strongly coimmunoprecipitated with parkin at 4degreesC in the presence of colchicine, a condition in which tubulin exits as alpha/beta heterodimers. At the subcellular level, parkin exhibited punctate immunostaining along microtubules in rat brain sections, cultured primary neurons, glial cells, and cell lines. This pattern of subcellular localization was abolished in cells treated with the microtubule-depolymerizing drug colchicine. The binding between parkin and tubulin apparently led to increased ubiquitination and accelerated degradation of alpha- and beta-tubulins in HEK293 cells. Similarly ubiquitinated tubulins were also observed in rat brain lysates. Furthermore, parkin mutants found in PD patients did not ubiquitinate or degrade either tubulin. Taken together, our results show that parkin is a novel tubulin-binding protein, as well as a microtubule-associated protein. Its ability to enhance the ubiquitination and degradation of misfolded tubulins may play a significant role in protecting neurons from toxins that cause PD.

Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW. 2005. Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicol Sci 88(1): 193-201.
Abstract: Paraquat, MPTP, and rotenone reproduce features of Parkinson's disease (PD) in experimental animals. The exact mechanisms by which these compounds damage the dopamine system are not firmly established, but selective damage to dopamine neurons and inhibition of complex I are thought to be involved. We and others have previously documented that the toxic metabolite of MPTP, MPP+, is transported into dopamine neurons through the dopamine transporter (DAT), while rotenone is not transported by DAT. We have also demonstrated the requirement for complex I inhibition and oxidative damage in the dopaminergic neurodegeneration produced by rotenone. Based on structural similarity to MPP+, it has been proposed that paraquat exerts selective dopaminergic toxicity through transport by the DAT and subsequent inhibition of mitochondrial complex I. In this study we report that paraquat is neither a substrate nor inhibitor of DAT. We also demonstrate that in vivo exposure to MPTP and rotenone, but not paraquat, inhibits binding of H-3-dihydrorotenone to complex I in brain mitochondria. Rotenone and MPP+ were both effective inhibitors of complex I activity in isolated brain mitochondria, while paraquat exhibited weak inhibitory effects only at millimolar concentrations. These data

indicate that, despite the apparent structural similarity to MPP+, paraquat exerts its deleterious effects on dopamine neurons in a manner that is unique from rotenone and MPTP.

Richardson JR, Sherer TB, Greenamyre JT, Miller GW. 2004. Screening of pesticides that inhibit complex I: Relevance to Parkinson's disease. Neurotoxicology 25(4):704.

Richter F, Hamann M, Richter A. 2005. Rotenone-induced alterations in mice: A suitable animal model of Parkinson's disease? Naunyn Schmiedebergs Arch Pharmacol 371:R79 .

Richter RJ, Furlong CE. 1999. Determination of paraoxonase (PON1) status requires more than genotyping. Pharmacogenetics 9(6):745-753.
Abstract: Human serum paraoxonase (PON1) is associated with high density lipoprotein (HDL) particles. This enzyme is involved in the metabolism of oxidized lipids and also plays a major role in the metabolism and detoxication of insecticides processed through the cytochrome P450/ PON1 pathway. An Arg/Gln (R/Q) substitution at position 192 determines a substrate dependent activity polymorphism, In addition to the effect of the amino acid substitution on rates of hydrolysis of different substrates, there is a large interindividual variability in the amount of PON1 protein in sera that is stable over time, Recently, a number of reports based solely on PON1 genotyping have suggested that in some populations, the PON1 (R192) allele may be a risk factor for coronary artery disease. Another report notes an increased risk of the PON1(R192) allele for Parkinson's disease. We report here the development of a two-dimensional, microtitre plate reader-based enzyme analysis that provides a high-throughput assessment of PON1 status. population distribution plots of diazoxonase Versus paraoxonase activities provides PON1 phenotype and an accurate inference of PON1 genotype. Both are important parameters for determining an individual's PON1 status, The analysis also provides PON1 allele frequencies for specific populations, Pharmacogenetics 9:745-753 (C) 1999 Lippincott Williams & Wilkins.

Rios C, Alvarezvega R, Rojas P. 1995. Depletion of copper and manganese in brain after mptp treatment of mice. Pharmacology & Toxicology 76(6): 348-352.
Abstract: The mechanism of action of MPTP, a parkinsonism-inducing drug has been related to trace metals as a result of the observed potentiation of the neurotoxic action of the drug when diethyldithiocarbamate is concurrently administered. Diethyldithiocarbamate is a well-known chelator of trace metals, particularly copper. In the present study we analyzed the concentrations of copper and manganese in four brain regions of mice treated with neurotoxic doses of MPTP, in order to further substantiate the relationship between trace metals of MPTP-induced neurotoxicity. Male Swiss albino mice were administered with MPTP (30 mg/kg) for either three or five days. Seven days after the last MPTP administration, they were sacrified and the content of manganese and copper in the following regions was determined by graphite furnace atomic absorption spectrophotometry:

cortex, cerebellum, midbrain and corpus striatum. Results indicate a significant depletion of manganese in corpus striatum (19.5% versus control) in the mice treated with MPTP for 5 days. Copper was also found to be decreased in corpus striatum (17.3% in mice treated for 3 days and 51.3% in mice treated for 5 days). Midbrain copper was depleted by 42.9% in the group of mice treated for 5 days with MPTP. Results indicate that MPTP induced a diminution of both copper and manganese in corpus striatum, suggesting that this alteration could be related to MPTP mechanism of action.

Ritz B, Yu F. 2000. Parkinson's disease mortality and pesticide exposure in California 1984-1994. Int J Epidemiol 29(2):323-329.
Abstract: Background In the last two decades reports from different countries emerged associating pesticide and herbicide use with Parkinson's disease (PD). California growers use approximately 250 million pounds of pesticides annually, about a quarter of all pesticides used in the US. Methods We employed a proportional odds mortality design to compare all cases of PD recorded as underlying (1984-1994) or associated causes (1984-1993) of death occurring in California with all deaths from ischaemic heart disease (ICD-9 410-414) during the same period. Based on pesticide use report data we classified California counties into several pesticide use categories. Agricultural census data allowed us to create measures of percentage of land per county treated with pesticides. Employing logistic regression models we estimated the effect of pesticide use controlling for age, gender, race, birthplace, year of deaths, and education. Results Mortality from PD as the underlying cause of death was higher in agricultural pesticide-use counties than in non-use counties. A dose response was observed for insecticide use per county land treated when using 1982 agricultural census data, but not for amounts of restricted pesticides used or length of residency in a country prior to death. Conclusions Our data show an increased PD mortality in California counties using agricultural pesticides, Unless all of our measures of county pesticide use are surrogates for other risk factors more prevalent in pesticide use counties, it seems important to target this prevalent exposure in rural California in future studies that use improved case finding mechanisms and collect pesticide exposure data for individuals.

Rocchitta G, Migheli R, Mura MP, Grella G, Esposito G, Marchetti B, Miele E, Desole MS, Miele M, Serra PA. 2005. Signaling pathways in the nitric oxide and iron-induced dopamine release in the striatum of freely moving rats: Role of extracellular Ca2+ and L-type Ca2+ channels. Brain Res 1047(1): 18-29.
Abstract: We showed previously that exogenous iron potentiated nitric oxide (NO) donor-induced release of striatal dopamine (DA) in freely moving rats, using microdialysis. In this study, the increase in dialysate DA induced by intrastriatal infusion of the NO-donor 3-morpholinosydnonimine (SIN-1, 1.0 mM for 180 min) was scarcely affected by Ca2+ omission. N-methyl-D-glucamine dithiocarbamate (MGD) is a thiol compound whose NO trapping activity is potentiated by iron(II). Intrastriatal co-infusion of MGD either alone or associated with iron(II), however, potentiated SIN-I-

induced increases in dialysate DA. In contrast, co-infusion of the NO trapper 4-(carboxyphenyl)4,4,5,5-tetramethylimidazole- 1-oxyl 3-oxide (carboxy-PTIO) significantly attenuated the increase in dialysate DA induced by SIN-1 (5.0 mM for 180 min). SIN-1 +MGD+iron(II)-induced increases in dialysate DA were inhibited by Ca2+ omission or co-infusion of either deferoxamine or the L-type (Ca-v 1.1 - 1.3) Ca2+ channel inhibitor nifedipine; in contrast, the increase was scarcely affected by co-infusion of the N-type (Ca-v 2.2) Ca2+ channel inhibitor omega-conotoxin GVIA. These results demonstrate that exogenous NO-induced release of striatal DA is independent on extracellular Ca2+; however, in presence of the NO trapper MGD, NO may preferentially react with either endogenous or exogenous iron to form a complex which releases striatal DA with an extracellular Ca2+-dependent and nifedipine-sensitive mechanism. (c) 2005 Elsevier B.V. All rights reserved.

Rodriguez VM, Thiruchelvam M, Cory-Slechta DA. 2005. Sustained exposure to the widely used herbicide atrazine: Altered function and loss of neurons in brain monoamine systems. Environ Health Perspect 113(6):708-715. Abstract: The widespread use of atrazine (ATR) and its persistence in the environment have resulted in documented human exposure. Alterations in hypothalamic catecholamines have been suggested as the mechanistic basis of the toxicity of ATR to hormonal systems in females and the reproductive tract in males. Because multiple catecholamine systems are present in the brain, however, ATR could have far broader effects than are currently understood. Catecholaminergic systems such as the two major long-length dopaminergic tracts of the central nervous system play key roles in mediating a wide array of critical behavioral functions. In this study we examined the hypothesis that ATR would adversely affect these brain dopaminergic systems. Male rats chronically exposed to 5 or 10 mg/kg ATR in the diet for 6 months exhibited persistent hyperactivity and altered behavioral responsivity to amphetamine. Moreover, when measured 2 weeks after the end of exposure, the levels of various monoamines and the numbers of tyrosine hydroxylase-positive (TH+) and -negative (TH-) cells measured using unbiased stereology were reduced in both doparninergic tracts. Acute exposures to 100 or 200 mg/kg ATR given intraperitoneally to evaluate potential mechanisms reduced both basal and potassium-evoked striatal dopamine release. Collectively, these studies demonstrate that ATR can produce neurotoxicity in doparninergic systems that are critical to the mediation of movement as well as cognition and executive function. Therefore, ATR may be an environmental risk factor contributing to dopaminergic system disorders, underscoring the need for further investigation of its mechanism(s) of action and corresponding assessment of its associated human health risks.

Rosenberg NL, Myers JA, Martin WR. 1989 Jan. Cyanide-induced parkinsonism: clinical, MRI, and 6-fluorodopa PET studies. Neurology 39(1):142-4. Abstract: A 46-year-old man ingested 1,500 mg of potassium cyanide in a suicide attempt. He survived, but later developed a severe parkinsonian syndrome. MRI revealed multiple areas of low-signal intensity in the globus pallidus and posterior putamen. A 6-fluorodopa PET study revealed

bilateral decreased uptake in the basal ganglia. This evidence of functional impairment of dopaminergic nigrostriatal neurons is related either to direct toxicity of cyanide or to the effects of cerebral hypoxia secondary to cyanide intoxication.

Rumsby PC, Brown T, Capleton AC, Rushton L, Koller KE, Levy LS. 2004. Pesticides and Parkinson's disease - a critical review. Toxicology 202(1-2): 71-72.

Rusyniak DE, Nanagas KA. 2004. Organophosphate poisoning. Semin Neurol 24 (2):197-204.
Abstract: Organophosphates are commonly used as pesticides around the world. Exposures to organophosphates cause a significant number of poisonings and deaths each year. Organophosphates bind and inhibit cholinesterase enzymes. Acute toxicity manifests as a cholinergic crisis with excessive glandular secretions, altered mental status, and weakness. Several delayed syndromes have also been associated with organophosphate exposure, including a myasthenic-like syndrome, peripheral neuropathies, neuropsychiatric abnormalities, and extrapyramidal disorders. Clinical features and management of organophosphate poisoning is reviewed with emphasis on those affecting the central and peripheral nervous system.

Ryu EJ, Harding HP, Angelastro JM, Vitolo OV, Ron D, Greene LA. 2002. Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease. J Neurosci 22(24):10690-10698.
Abstract: 6-Hydroxydopamine, 1-methyl-4-phenyl-pyridinium (MPP+), and rotenone cause the death of dopaminergic neurons in vitro and in vivo and are widely used to model Parkinson's disease. To identify regulated genes in such models, we performed serial analysis of gene expression on neuronal PC12 cells exposed to 6-hydroxydopamine. This revealed a striking increase in transcripts associated with the unfolded protein response. Immunoblotting confirmed phosphorylation of the key endoplasmic reticulum stress kinases IRE1alpha and PERK (PKR-like ER kinase) and induction of their downstream targets. There was a similar response to MPP+ and rotenone, but not to other apoptotic initiators. As evidence that endoplasmic reticulum stress contributes to neuronal death, sympathetic neurons from PERK null mice in which the capacity to respond to endoplasmic reticulum stress is compromised were more sensitive to 6-hydroxydopamine. Our findings, coupled with evidence from familial forms of Parkinson's disease, raise the possibility of widespread involvement of endoplasmic reticulum stress and the unfolded protein response in the pathophysiology of this disease.

Sagi Y, Drigues N, Youdim MBH. 2005. The neurochemical and behavioral effects of the novel cholinesterase-monoamine oxidase inhibitor, ladostigil, in response to L-dopa and L-tryptophan, in rats. Br J Pharmacol 146(4): 553-560.
Abstract: 1 The novel drugs, ladostigil (TV3326) and TV3279, are R and S isomers, respectively, derived from a combination of the carbamate

cholinesterase (ChE) inhibitor, rivastigmine, and the pharmacophore of the monoamine oxidase (MAO) B inhibitor, rasagiline. They were developed for the treatment of comorbidity of dementia with Parkinsonism. In the present study, we determined the effects of these drugs on both aminergic neurotransmitter levels and motor behavioral activity in naive and in L-dopa- or L-tryptophan-induced rats. 2 Chronic treatment of rats with ladostigil (52 mg kg(-1) for 21 days) inhibited hippocampal and striatal MAO A and B activities by > 90%, increased striatal levels of dopamine and serotonin, and inhibited striatal ChE activity by similar to 50%. 3 Chronic TV3279 (26 mg kg(-1) for 21 days) similarly inhibited similar to 50% of striatal ChE activity, but did not affect MAO activity or amine levels. 4 In sharp contrast to the inductive effect of the MAO A/B inhibitor, tranylcypromine (TCP), on stereotyped hyperactivity in response to L-dopa (50 mg kg(-1)) or L-tryptophan (100 mg kg(-1)), ladostigil completely inhibited these behavioral hyperactivity syndromes. Accordingly, acute rivastigmine (2 mg kg(-1)) and chronic TV3279 abolished the ability of TCP to initiate L-dopa-induced hyperactivity, while scopolamine (0.5 mg kg(-1)) reversed the inhibitory effect of chronic ladostigil on L-dopa-induced hyperactivity, suggesting that ladostigil may attenuate successive locomotion by activating central cholinergic muscarinic receptors. 5 Finally, while chronic ladostigil administration to naive rats resulted in preserved spontaneous motor behavior, acute treatment with ladostigil decreased motor performance, compared to control animals. In contrast, chronic as well as acute treatments with TV3279 reduced spontaneous motor activity. Thus, the aminergic potentiation by ladostigil may counteract its cholinergic inhibitory effect on spontaneous motor behavior. 6 Our results suggest that potentiation of both aminergic and cholinergic transmission systems by ladostigil contributes equally to motor behavior performance, which is substantially impaired in comorbidity of dementia with Parkinsonism including dementia with Lewy bodies (DLB).

Sagi Y, Weinstock M, Youdim MBH. 2003. Attenuation of MPTP-induced dopaminergic neurotoxicity by TV3326, a cholinesterase-monoamine oxidase inhibitor. J Neurochem 86(2):290-297.
Abstract: (R)-[(N -propargyl-(3R ) aminoindan-5-yl) ethyl methyl carbamate] (TV3326) is a novel cholinesterase and brain-selective monoamine oxidase (MAO)-A/-B inhibitor. It was developed for the treatment of dementia co-morbid with extra pyramidal disorders (parkinsonism), and depression. On chronic treatment in mice it attenuated striatal dopamine depletion induced by MPTP and prevented the reduction in striatal tyrosine hydroxylase activity, like selective B and non-selective MAO inhibitors. TV3326 preferentially inhibits MAO-B in the striatum and hippocampus, and the degree of MAO-B inhibition correlates with the prevention of MPTP-induced dopamine depletion. Complete inhibition of MAO-B is not necessary for full protection from MPTP neurotoxicity. Unlike that seen after treatment with other MAO-A and -B inhibitors, recovery of striatal and hippocampal MAO-A and -B activities from inhibition by TV3326 did not show first-order kinetics. This has been attributed to the generation of a number of metabolites by TV3326 that cause differential inhibition of

these enzymes. Inhibition of brain MAO-A and -B by TV3326 resulted in significant elevations of dopamine, noradrenaline and serotonin in the striatum and hippocampus. This may explain its antidepressant-like activity, resembling that of moclobemide in the forced-swim test in rats.

Sakka N, Sawada H, Izumi Y, Kume T, Katsuki H, Kaneko S, Shimohama S, Akaike A. 2003. Dopamine is involved in selectivity of dopaminergic neuronal death by rotenone. Neuroreport 14(18):2425-2428.
Abstract: Mitochondrial complex I activity is partially suppressed in patients with Parkinson's disease, which is characterized by dopaminergic neuronal death. However, the precise relationship between neuronal death and mitochondrial complex I suppression has been unresolved. We investigated the involvement of superoxide and endogenous dopamine in neurotoxicity by rotenone, a complex I inhibitor. A short exposure to rotenone at high concentrations reduced the viability of both dopaminergic and non-dopaminergic neurons. The toxicity was significantly prevented by a membrane-permeable superoxide dismutase mimetic and alpha-methyl-p-tyrosine (alpha-MT), a tyrosine hydroxylase inhibitor. Chronic treatment with low-concentration rotenone caused selective toxicity to dopaminergic neurons, and this toxicity was attenuated by alpha-MT These data suggest that superoxide and endogenous dopamine play an important role in dopaminergic neuronal loss. (C) 2003 Lippincott Williams Wilkins.

Sala M, Sunyer J, Otero R, Santiago-Silva M, Ozalla D, Herrero C, To-Figueras J, Kogevinas M, Anto JM, Camps C, Grimalt J. 1999. Health effects of chronic high exposure to hexachlorobenzene in a general population sample. Arch Environ Health 54(2):102-109.
Abstract: Hexachlorobenzene, an organochlorine compound that accumulates in humans, is widespread throughout the environment. In this study, we describe the health status of inhabitants of a rural village that surrounds an electrochemical factory characterized by high levels of hexachlorobenzene in the air. During 1994, we conducted a cross-sectional study of 1 800 inhabitants in the south of Catalonia, Spain, who were older than 14 y of age. We obtained information on lifestyles and occupational and medical histories via questionnaire. Self-reported health outcomes were validated against clinical records and cancer registry data. Serum revels of hexachlorobenzene were very high in males who worked in the electrochemical factory (geometric mean = 54.6 ng/ml in randomized participants). Levels were lower among subjects who had never worked in the electrochemical factory (females, 14.9 ng/ml; males, 9.0 ng/ml). Levels of other organochlorine compounds (i.e., beta-hexachlorocyclohexane, 2,2-bis[p-chlorophenyl]-1,1-dichloroethylene) were in the same range found in of her communities, Perceived health, prevalence of self-reported common chronic conditions, and porphyria cutanea tarda, thyroid pathology, Parkinson's disease, cancer, and reproductive outcomes were within the ranges observed in other studies. Employment in the plant, however, was associated with having any of the a priori selected health outcomes that were potentially related to exposure to hexachlorobenzene (odds ratio for cancer prevalence = 1.9; 95% confidence interval = 0.5, 7.6). Our population of workers and nonworkers

had the highest revels of hexachlorobenzene ever described. The results suggest that exposure to hexachlorobenzene did not affect the general health status of the this population, but it was associated with specific health effects of the most highly exposed subjects.

Salach JI, Singer TP, Castagnoli N Jr, Trevor A. 1984 Dec 14. Oxidation of the neurotoxic amine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by monoamine oxidases A and B and suicide inactivation of the enzymes by MPTP. Biochem Biophys Res Commun 125(2):831-5.
Abstract: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a thermal breakdown product of a meperidine-like narcotic analgetic used by drug abusers as a synthetic heroin, causes Parkinsonian symptoms in humans and degeneration of the substantia nigra in monkeys. MPTP is oxidized by brain mitochondrial preparations in a process which is blocked by deprenyl and pargyline, implying catalysis by monoamine oxidase B. The present paper demonstrates that pure MAO B isolated from beef liver oxidizes MPTP 38% as fast as benzylamine with a comparable Km value. Additionally, MAO A, isolated from human placenta, oxidizes MPTP to the same product at about 12% of the rate of kynuramine, again with a comparable Km value. The latter reaction is blocked by clorgyline. Both forms of MAO are progressively inactivated by MPTP by a process which follows first order kinetics. This progressive inactivation and the fact that the activity of MAO B is not significantly regenerated following gel exclusion chromatography suggest the formation of a covalent adduct with enzyme. Thus, MPTP appears to be a suicide inactivator of MAO.

Salvi RM, Lara DR, Ghisolfi ES, Portela LV, Dias RD, Souza DO. 2003. Neuropsychiatric evaluation in subjects chronically exposed to organophosphate pesticides. Toxicol Sci 72(2):267-271.
Abstract: Long-term exposure to low levels of organophosphate pesticides (OP) may produce neuropsychiatric symptoms. We performed clinical, neuropsychiatric, and laboratory evaluations of 37 workers involved in family agriculture of tobacco from southern Brazil who had been exposed to OP for 3 months, and in 25 of these workers, after 3 months without exposure to OP. Plasma acetylcholinesterase activity levels of all subjects were within the normal range (3.2 to 9.0 U/I) and were not different between on- and off-exposure periods (4.7 +/- 0.9 and 4.5 +/- 1.1 U/l, respectively). Clinically significant extrapyramidal symptoms were present in 12 of 25 subjects, which is unexpected in such a population. There was a significant reduction of extrapyramidal symptoms after 3 months without exposure to OP, but 10 subjects still had significant parkinsonism. Mini-mental and word span scores were within the expected range for this population and were not influenced by exposure to OP. Eighteen of the 37 subjects (48%) had current psychiatric diagnoses in the first interview (13 with generalized anxiety disorder and 8 with major depression). Among the 25 subjects who completed both evaluations, the total number of current psychiatric diagnoses, after 3 months without using OP, dropped from 24 to 13 and the number of affected individuals with any psychiatric diagnosis dropped from 11 to 7. In conclusion, this study reinforces the need for parameters other than acetylcholinesterase activity to monitor for chronic

consequences of chronic low-dose OP exposure, and it suggests that subjects have not only transient motor and psychiatric consequences while exposed, but may also develop enduring extrapyramidal symptoms.

Sanborn MD, Cole D, Abelsohn A, Weir E. 2002. Identifying and managing adverse environmental health effects: 4. Pesticides. Can Med Assoc J 166 (11):1431-1436.
Abstract: PESTICIDE EXPOSURE CAN CAUSE MANY DIFFERENT HEALTH EFFECTS, from acute problems such as dermatitis and asthma exacerbation to chronic problems such as chronic obstructive pulmonary disease and cancer. The resulting clinical presentations are undifferentiated, and specific knowledge of the links to environmental exposures is often required for effective diagnosis. In this article we illustrate the use of the (CHOPD2)-O-2 mnemonic (Community, Home, Hobbies, Occupation, Personal habits, Drugs and Diet), a history-taking tool that assists physicians in quickly identifying possible environmental exposures. We also provide clinical information on the epidemiology, clinical presentations, treatment and prevention of pesticide exposures.

Sanchez-Ramos J, Facca A, Basit A, Song SJ. 1998. Toxicity of dieldrin for dopaminergic neurons in mesencephalic cultures. Exp Neurol 150(2): 263-271.
Abstract: Dieldrin can be retained for decades in lipid-rich tissue and has been measured in some postmortem PD brains. Dieldrin has been reported to deplete brain monoamines in several species and has been shown to inhibit mitochondrial respiration. To further investigate the possibility that it may be involved in the pathogenesis of parkinsonism, its toxicity for dopaminergic (DA) neurons was assessed in a mesencephalic cell culture model. Primary neuronal cultures of mesencephalic neurons were prepared from fetal rats or fetal mice, grown for 1 week and incubated with Dieldrin (0.01-100 mu M) for 24 or 48 h. Toxicity for DA neurons was determined by measuring density of surviving tyrosine hydroxylase immunoreactive (TH-ir) cells. Toxicity for gamma-aminobutyric acid (GABA)-ergic neurons was determined by measuring survival of glutamate decarboxylase (GAD)-ir neurons. General, nonselective cytotoxicity was determined by counting cells visualized by phase contrast microscopy or by DAPI-stained cells with fluorescence microscopy. Dieldrin exposure for 24 h resulted in a dose-dependent decrease in survival of TH-IR cells (DA neurons) with a 50% decrease (EC50) produced by 12 mu M in rat mesencephalic cultures. Dieldrin also produced a dose-and time-dependent decrease in mouse DA-ergic and GABA-ergic neurons in mouse mesencephalic cultures. GABA-ergic neurons were less sensitive to the toxin compared to DA-ergic neurons. Cellular uptake of H-3-DA was also affected by lower concentrations of Dieldrin (EC50 = 7.98 mu M) than up-take of H-3-GABA (EC50 = 43 mu M) Thus, Dieldrin appears to be a relatively selective DA-ergic neurotoxin in mesencephalic cultures. Dieldrin, which may be ubiquitous in the environment, is proposed as an agent which can initiate and promote dopaminergic neurodegeneration in susceptible individuals. (C) 1998 Academic Press.

Sanchez-Reus MI, Peinado II, Molina-Jimenez MF, Benedi J. 2005. Fraxetin prevents rotenone-induced apoptosis by induction of endogenous glutathione in human neuroblastoma cells. Neurosci Res 53(1):48-56. Abstract: Fraxetin belongs to an extensive group of natural phenolic anti-oxidants. In the present study, using a human neuroblastoma SH-SY5Y cells, we have investigated the protective effects of this compound on modifications in endogenous reduced glutathione (GSH), intracellular oxygen species (ROS) and apoptotic death on rotenone-mediated cytoxicity. Incubation of cells with the fraxetin led to a significant elevation dose-dependent of cellular GSH and this was accompanied by a marked protection against rotenone-mediated toxicity, which was also significantly reversed in the cells with buthionine sulfoximine (BSO) co-treatment. Taken together, this study suggested that intracellular GSH appeared to be an important factor in fraxetin-mediated cytoprotection against rotenone-toxicity in SH-SY5Y cells. Fraxetin at 10-100 mu M inhibited the formation of ROS, cytochrome c release, activation of caspase-3 and 9, and suppressed the up-regulation of Bax, whereas no significant change occurred in Bcl-2 levels. Our results indicated that the anti-oxidative and anti-apoptotic properties render this natural compound potentially protective against rotenone-induced cytotoxicity. (c) 2005 Elsevier Ireland Ltd and the Japan Neuroscience Society. All rights reserved.

Sanchezramos JR, Factor SA, Weiner WJ. 1987. Paraquat and parkinsons-disease - reply. Neurology 37(11):1820-1821.

Sanchezramos JR, Hefti F, Weiner WJ. 1987. Paraquat and parkinsons-disease. Neurology 37(4):728.

Saravanan KS, Sindhu KM, Mohanakumar KP. 2003. L-deprenyl attenuates the rotenone-induced dopaminergic neurotoxicity: experimental evidences in rats. J Neurochem 87:106.

Saravanan KS, Sindhu KM, Mohanakumar KP. 2005. Acute intranigral infusion of rotenone in rats causes progressive biochemical lesions in the striatum similar to Parkinson's disease. Brain Res 1049(2):147-155. Abstract: We examined in Sprague-Dawley rats whether intranigral administration of complex-I inhibitor, rotenone, produces biochemical lesions in the striatum similar to those observed in Parkinson's disease (PD). Unilateral stereotaxic infusion of rotenone (2-12 mu g in 1 mu 1) into substantia nigra (SN) pars compacta caused significant inhibition of complex-I activity and increased production of hydroxyl radicals in vivo as measured employing spectrophotometric and HPLC-clectrochemical procedures, respectively. It also caused a significant time- and dose-dependent reduction of dopamine level, but not scrotonin, in the ipsilateral striatum when assayed using an HPLC electrochemical method. This effect was found to be progressive for 90 days. A dose-dependent decrease in nigral glutathione level, as measured fluorimetrically, was also observed to be progressive till 90th day. A significant decrease in tyrosine hydroxylase immunoreactivity in the striatum (73 +/- 8.4% as assessed by densitometric studies) or in SN ipsilateral to the side of infusion suggested

nigrostriatal neuronal degeneration. A dose of rotenone (6 mu g in 1 mu l) that caused 55% striatal dopamine depletion when infused into the SN failed to affect serotonin levels in the terminal regions when infused into the nucleus raphe dorsalis, indicating rotenone's specificity of action towards dopaminergic neurons. Our findings suggest that unilateral infusion of rotenone reproduces neurochemical and neuropathological features of hemiparkinsonism in rats and indicate an active involvement of oxidative stress in rotenone-induced nigrostriatal neurodegeneration. The present study also demonstrates more sensitivity of dopaminergic neurons towards rotenone and establishes mitochondrial complex-I damage as one of the major contributory components of neurodegeneration in PD. The progressive nature of pathology in this model closely mimics idiopathic PD, and absence of mortality warrants the use of this model in drug discovery programs. (c) 2005 Elsevier B.V. All rights reserved.

Sasaki T, Soga S, Ishii S, Kobayashi T, Nagai H, Senda M. 1999. Visualization of mitochondrial oxygen fixation in brain slices by gas-tissue autoradiography. Brain Res 831(1-2):263-272.
Abstract: We have developed a novel autoradiographic method of visualizing oxygen fixation with sufficient delivery of [O-15]O-2/O-2. Brain slices (400 mu m) were preincubated in Krebs-Ringer phosphate buffer and exposed to [O-15]O-2 in a chamber. Fixation of [O-15]O-2 correlated with the polarographically measured oxygen consumption among tissue slices from various organs (r = 0.84). The fixation of [O-15]O-2 by brain slices was significantly reduced (7.2% of the control) by heat-treatment or dose dependently by NaCN (18.2% of the control on 50 mM NaCN pretreatment). The O-15 radioactivity in the brain slices prepared from rotenone injected rats was also reduced compared to the control (56.8% of the control side). In an autoradiographic study,O-15 radioactivity showed a heterogeneous distribution both in coronal and sagittal sections. Autoradiography of young and senescent rat brain sections showed reduction of oxygen uptake with aging in the cerebrum, the senescent being 77.4% of the young. This method provides information regarding basic oxygen consumption of tissue slices under condition of sufficient O-2 delivery, which reflects mitochondrial electron transport. (C) 1999 Elsevier Science B.V. All rights reserved.

Satoh T, Sakai N, Enokido Y, Uchiyama Y, Hatanaka H. 1996. Survival factor-insensitive generation of reactive oxygen species induced by serum deprivation in neuronal cells. Brain Res 733(1):9-14.
Abstract: To investigate the involvement of reactive oxygen species (ROS) in neuronal apoptosis, we performed confocal and flow cytometric analysis with a ROS-specific fluorogen, 6-carboxy-2',7'-dichorodihydrofluorescein diacetate, di(acetoxymethyl ester) (C-DCDHF-DA). Serum deprivation significantly increased the level of ROS in PC12 cells and rat cortical neurons. N,N'-diphenyl-p-phenylenediamine (DPPD), an antioxidant, reduced ROS production induced by serum deprivation and recovered cell survival. However, some survival factors such as nerve growth factor and Bcl-2, which prevented the apoptosis of PC12 cells, did not affect the up-regulation of ROS induced by serum deprivation. Epidermal growth factor

which prevented the apoptosis of cortical neurons, did not affect the increase of ROS. These data suggest that survival factors rescue the serum deprivation-induced apoptosis independently of ROS production.

Savolainen J, Leppanen J, Forsberg M, Taipale H, Nevalainen T, Huuskonen J, Gynther J, Mannisto PT, Jarvinen T. 2000. Synthesis and in vitro/in vivo evaluation of novel oral N-alkyl- and N,N-dialkyl-carbamate esters of entacapone. Life Sci 67(2):205-216.
Abstract: Entacapone has a relatively low oral bioavailability which may, in part, be due to its low aqueous solubility at low pH and/or its hydrophilic character at neutral pH. Various novel N-alkyl and N,N-dialkyl carbamate esters of entacapone were synthesized as possible prodrugs of entacapone in order to increase its aqueous solubility at an acidic pH and to increase its lipophilicity at neutral pH. Oral bioavailability of entacapone and selected carbamate esters were investigated in rats. Both N-alkyl and N,N-dialkyl carbamate esters were relatively stable against chemical hydrolysis at pH 7.4 (t(1/2) = 14.9-20.7 h), but hydrolyzed rapidly (t(1/2) = 0.8-2.7 h) in human serum. However, in contrast to N-alkyl carbamates, N,N-dialkyl carbamates did not release entacapone in in vitro enzymatic hydrolysis (human serum) studies. N-Alkyl carbamates, 2a-c, showed increased aqueous solubility at pH 7.4, of which 2a and 2c also show increased aqueous solubility at pH 5.0, compared to entacapone, In addition to increased aqueous solubility, 2c showed increased lipophilicity at pH 7.4. However, two N-alkyl carbamates of entacapone did not increase the oral bioavailability of the parent drug in rats. Thus, it can be concluded that the relatively low lipophilicity of entacapone is not the cause of its low bioavailability. (C) 2000 Elsevier Science Inc. All rights reserved.

Sawada H, Kohno R, Kihara T, Izumi Y, Sakka N, Ibi M, Nakanishi M, Nakamizo T, Yamakawa K, Shibasaki H, Yamamoto N, Akaike A, Inden M, Kitamura Y, Taniguchi T, Shimohama S. 2004. Proteasome mediates dopaminergic neuronal degeneration, and its inhibition causes alpha-synuclein inclusions. J Biol Chem 279(11):10710-10719.
Abstract: Parkinson's disease is characterized by dopaminergic neuronal death and the presence of Lewy bodies. alpha-Synuclein is a major component of Lewy bodies, but the process of its accumulation and its relationship to dopaminergic neuronal death has not been resolved. Although the pathogenesis has not been clarified, mitochondrial complex I is suppressed, and caspase-3 is activated in the affected midbrain. Here we report that a combination of 1-methyl-4-phenylpyridinium ion (MPP+) or rotenone and proteasome inhibition causes the appearance of alpha-synuclein-positive inclusion bodies. Unexpectedly, however, proteasome inhibition blocked MPP+- or rotenone-induced dopaminergic neuronal death. MPP+ elevated proteasome activity, dephosphorylated mitogen-activating protein kinase ( MAPK), and activated caspase-3. Proteasome inhibition reversed the MAPK dephosphorylation and blocked caspase-3 activation; the neuroprotection was blocked by a p42 and p44 MAPK kinase inhibitor. Thus, the proteasome plays an important role in both inclusion body formation and dopaminergic neuronal death but these processes form

opposite sides on the proteasome regulation in this model.

Schantz SL, Sweeney AM, Gardiner JC, Humphrey HEB, Mccaffrey RJ, Gasior DM, Srikanth KR, Budd ML. 1996. Neuropsychological assessment of an aging population of Great Lakes fisheaters. Toxicol Ind Health 12(3-4):403-417. Abstract: Because of the decline in central nervous system function that occurs with age, older people may be at greater risk of neurological dysfunction following exposure to neurotoxic contaminants in the environment. This study was designed to assess the neuropsychological functioning of a group of 50-90-year-old fisheaters exposed to polychlorinated biphenyls (PCBs) through Great Lakes fish consumption, and a group of age- and sex-matched nonfisheaters selected from the Michigan Department of Public Health's established cohort of fisheaters and nonfisheaters. A neuropsychological assessment battery, demographic interview, and fish consumption questionnaire were developed and piloted on similarly aged men and women in the Lansing and Detroit, Michigan, areas. The assessment battery included tests of motor function, memory and learning, executive functions, and visual-spatial functions, and took approximately two hours to administer. Most of the tests included in the battery have been shown to be sensitive to subtle, age-related declines in cognitive and motor function. The demographic questionnaire included questions on a number of important control variables that could influence the neuropsychological end points that were assessed in the study. These included demographic background alcohol consumption,, tobacco use, prescription and nonprescription drug use, medical history (including psychiatric illnesses), employment history, and activity level. The fish consumption questionnaire asked about historical and current consumption of specific fish species from each of the Great Lakes and its tributaries and was based on the fish consumption advisories published in the 1992 Michigan Fishing Guide. The questionnaire also asked about consumption of wild game, fish preparation and cooking methods, serving size, and changes in fish consumption patterns over time. After each subject completed the neuropsychological assessment, demographic interview, and fish consumption questionnaire, a blood sample was collected for analysis of PCBs, dichloro diphenyl dichloroethene (DDE), and ten other contaminants frequently detected in Great Lakes fish. Subject recruitment for the study began in July 1993 and was completed in November 1995. The data will be analyzed in two steps: first, to assess differences in confounding variables between fisheaters and nonfisheaters; and secondly, to determine the independent effects of Great Lakes fish consumption, as well as serum PCB and DDE levels, on cognitive and motor function after controlling for all identified covariates. Three indices of PCB exposure-total PCBs, total ortho-substituted PCBs and total coplanar PCBs-will be assessed. These studies should shed light on three questions: 1) Does consumption of contaminated fish from the Great Lakes exacerbate or accelerate the normal age-related decline in cognitive and motor function? 2) Do serum PCB or DDE concentrations predict the degree of behavioral dysfunction? and 3) If PCB exposure is related to behavioral outcomes, which class of PCB congeners, ortho-substituted or coplanar, are

responsible for the cognitive and motor deficit?

Schapira AHV. 2002. Dopamine agonists and neuroprotection in Parkinson's diseae. Eur J Neurol 9:7-14.
Abstract: Dopamine agonists are effective in reversing the motor sympthoms of Parkinson's disease (PD). They have also shown that they can delay or prevent the onset of motor complications associated with levodopa use. Recent attention has focused on the possible role for dopamine agonists in neuroprotection. Numerous studies have demonstrated that a variety of dopamine agonists can protect dopaminergic neuronal function in several toxin model systems. Pramipexole in particular has shown efficacy in reducing toxicity to MPTP, MPP, rotenone and 6-hydroxydopamine. Recent studies in early PD using imaging parameters as a surrogate marker of dopaminergic neuronal integrity have shown that pramipexole and ropinirole can apparently retard the rate of cell loss. These observations are of considerable interest, but additional studies are required to confirm a neuroprotective function for these dopamine agonists.

Schapira AHV. 2002. Neuroprotection and dopamine agonists. Neurology 58 (4):S9-S18.
Abstract: Several factors are known to be capable of inducing relatively selective dopaminergic cell death in the substantia nigra and inducing the clinical features that characterize Parkinson's disease (PD). Neuronal toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can induce parkinsonism in human and animal models, and rotenone, another specific mitochondrial complex I inhibitor, can induce similar effects in rodents to produce a model for PD. Studies in twins suggest a significant genetic component to young-onset PD, and several gene mutations have now been identified as causing familial autosomal dominant or autosomal recessive PD. Etiologic factors including free radical-mediated damage (including excitotoxicity), mitochondrial dysfunction, and inflammation-mediated cell damage can contribute to pathogenesis. In addition, the recent interest in protein misfolding, aggregation, and proteosomal activity has provided further insight into potential pathogenetic pathways in PD. Against this background there has been increasing interest in the development of drugs to modify these biochemical abnormalities and thus alter the course of PD, either by retarding the rate of cell death or by restoring function to neurons that are likely to be damaged but not dead. In this context, dopamine agonists have shown significant promise. Not only do these drugs provide symptomatic relief of PD but they also appear to be associated with a significant decrease in the rate of motor complications and to be capable of protecting against some of the adverse consequences of levodopa use. However, evidence is now emerging that dopamine agonists may have additional neuroprotective properties. As a group, they have antioxidant actions in vitro and in vivo. More specifically, the D-2/D-3 dopamine agonist pramipexole may have neuroprotective activity that is, at least in part, unrelated to its dopamine agonist action. Protection in cell and animal models against a variety of toxins, including MPTP and 6-hydroxydopamine, confirms that this agonist has in vitro and in vivo

neuroprotective action, Evidence is now emerging that some of this may be mediated by direct action on mitochondrial membrane potential and the inhibition of apoptosis. If the neuroprotective action of this drug is confirmed in patients with PD, this will have important implications for its early use in patients.

Schneckenburger H, Gschwend MH, Sailer R, Strauss WSL, Lyttek M, Stock K, Zipfl P. 2000. Time-resolved in situ measurement of mitochondrial malfunction by energy transfer spectroscopy. Journal of Biomedical Optics 5(4):362-366.
Abstract: To establish optical in situ detection of mitochondrial malfunction, nonradiative energy transfer from the coenzyme NADH to the mitochondrial marker rhodamine 123 (R123) was examined. Dual excitation of R123 via energy transfer from excited NADH molecules as well as by direct absorption of light results in two fluorescence signals whose ratio is a measure of mitochondrial NADH. A screening system was developed in which these signals are detected simultaneously using a time-gated (nanosecond) technique for energy transfer measurements ana a frequency selective technique for direct excitation and fluorescence monitoring of R123, Optical and electronic components of the apparatus are described, and results obtained from cultivated endothelial cells are reported. The ratio of fluorescence intensities excited in the near ultraviolet and blue-green spectral ranges increased by a factor 1.5 or 1.35 after inhibition of the mitochondrial respiratory chain by rotenone at cytotoxic or noncytotoxic concentrations, respectively. Concomitantly the amount of mitochondrial NADH increased. Excellent linearity between the number of cells incubated with R123 and fluorescence intensity was found in suspension. (C) 2000 Society of Photo-Optical Instrumentation Engineers. [S1083-3668(00)00504-9].

Schober A. 2004. Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. Cell Tissue Res 318(1):215-224.
Abstract: Neurological disorders in humans can be modeled in animals using standardized procedures that recreate specific pathogenic events and their behavioral outcomes. The development of animal models of Parkinson's disease (PD) is important to test new neuroprotective agents and strategies. Such animal models of PD have to mimic, at least partially, a Parkinson-like pathology and should reproduce specific features of the human disease. PD is characterized by massive degeneration of dopaminergic neurons in the substantia nigra, the loss of striatal dopaminergic fibers and a dramatic reduction of the striatal dopamine levels. The formation of cytoplasmic inclusion bodies ( Lewy bodies) in surviving dopaminergic neurons represents the most important neuropathological feature of PD. Furthermore, the massive striatal dopamine deficiency causes easily detectable motor deficits in PD patients, including bradykinesia, rigidity, and resting tremor, which are the cardinal symptoms of PD. Over the years, a broad variety of experimental models of PD were developed and applied in diverse species. This review focuses on the two most common "classical" toxin-induced PD models, the 6-hydroxy- dopamine (6-OHDA model) and the 1-methyl-4-phenyl- 1,2,3,6-

tetrahydropyridine (MPTP) model. Both neurotoxins selectively and rapidly destroy catecholaminergic neurons, whereas in humans the PD pathogenesis follows a progressive course over decades. This discrepancy reflects one important and principal point of weakness related to most animal models. This review discusses the most important properties of 6-OHDA and MPTP, their modes of administration, and critically examines advantages and limitations of selected animal models. The new genetic and environmental toxin models of PD (e.g. rotenone, paraquat, maneb) are discussed elsewhere in this "special issue."

Schulte PA, Burnett CA, Boeniger MF. 1996. Neurodegenerative diseases: Occupational occurrence and potential risk factors, 1982 through 1991. Am J Public Health 86(9):1281-1288.
Abstract: Objectives. To identify potential occupational risk factors, this study examined the occupational occurrence of various neurodegenerative diseases. Methods. Death certificates from 27 states in the National Occupational Mortality Surveillance System were evaluated for 1982 to 1991. Proportionate mortality ratios were calculated by occupation for presenile dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease. Results. Excess mortality was observed for all four categories in the following occupational categories: teachers; medical personnel; machinists and machine operators; scientists; writers/ designers/entertainers; and support and clerical workers. Clusters of three neurodegenerative diseases were also found in occupations involving pesticides, solvents, and electromagnetic fields and in legal, library, social, and religious work, Early death from motor neuron disease was found for firefighters, janitors, military personnel, teachers, excavation machine operators, and veterinarians, among others. Conclusions. Neurodegenerative disease occurs more frequently in some occupations than in others, and this distribution, which may indicate Occupational risk factors, should be further investigated.

Scott WK, Zhang L, Stajich JM, Scott BL, Stacy MA, Vance JM. 2004. Pesticide use and risk of Parkinson disease: A family-based case-control study. Mov Disord 19:S196 .

Seaton TA, Cooper JM, Schapira AHV. 1997. Free radical scavengers protect dopaminergic cell lines from apoptosis induced by complex I inhibitors. Brain Res 777(1-2):110-118.
Abstract: The cause of dopaminergic neurodegeneration in Parkinson's disease remains unclear, but may involve both oxidative stress and mitochondrial complex I inhibition. We have demonstrated that complex I inhibitors, including rotenone, MPP+, isoquinoline and tetrahydroisoquinoline, induce apoptosis in PC12 and SK-N-MC dopaminergic cell lines which was decreased by pretreatment with N-acetylcysteine, TEMPO, dihydrolipoic acid or pyrrolidine dithiocarbamate. These results indicate that the pathway leading to apoptosis following complex I inhibition involves free radical generation. The free radical generation may result directly from inhibition of the mitochondrial respiratory chain or indirectly juring the apoptotic process itself. This has

important implications for our understanding of the relationship between complex I deficiency and oxidative stress and neurodegeneration in Parkinson's disease. (C) 1997 Elsevier Science B.V.

Seaton TA, Cooper JM, Schapira AHV. 1998. Cyclosporin inhibition of apoptosis induced by mitochondrial complex I toxins. Brain Res 809(1):12-17.
Abstract: The cause of dopaminergic cell death in Parkinson's disease (PD) remains unknown, but may involve oxidative stress and mitochondrial complex I deficiency. Opening of the permeability transition pore and disruption of the mitochondrial transmembrane potential are known to be common events in the apoptotic pathway. Cyclosporin A and its non-immunosuppressant analogue, N-methyl-4-valine cyclosporin inhibit the opening of the mitochondrial megachannel. Complex I inhibitors, including MPP+, are known to induce both apoptosis in cell culture and parkinsonism in man and other primates. The present study using propidium iodide and FITC-TUNEL staining to identify apoptotic cells, demonstrates that rotenone, MPP+ and tetrahydroisoquinoline induce apoptosis in PC12 cells. Apoptosis induced by these agents was decreased by cyclosporin A and N-methyl-4-valine cyclosporin. Thus, apoptosis induced by inhibitors of mitochondrial complex I is probably mediated by permeability pore opening and collapse of the mitochondrial membrane potential. This observation may allow the development of novel neuroprotective strategies in disorders that may involve mitochondrial dysfunction and apoptotic cell death. (C) 1998 Elsevier Science B.V. All rights reserved.

Sechi GP, Agnetti V, Piredda M, Canu M, Deserra F, Omar HA, Rosati G. 1992. Acute and persistent parkinsonism after use of diquat. Neurology 42(1): 261-263.

Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. 1996. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: A case-control study in Germany. Neurology 46(5):1275-1284.
Abstract: In a case-control study, we investigated the possible etiologic relevance to Parkinson's disease (PD) of rural factors such as farming activity, pesticide exposures, well-water drinking, and animal contacts; toxicologic exposures such as wood preservatives, heavy metals, and solvents; general anesthesia; head trauma; and differences in the intrauterine environment. We recruited 380 patients in nine German clinics, 379 neighborhood control subjects, and 376 regional control subjects in the largest case-control study investigating such factors and collected data in structured personal interviews using conditional logistic regression to control for educational status and cigarette smoking. The latter was strongly inversely associated with PD. There were significantly elevated odds ratios (OR) for pesticide use, in particular, for organochlorines and alkylated phosphates, but no association was present between PD and other rural factors, A significantly elevated OR was present for exposure to wood preservatives. Subjective assessment by the probands indicated that exposure to some heavy metals, solvents, exhaust fumes, and carbon monoxide was significantly more frequent among patients than control

subjects, but this was not confirmed by a parallel assessment of job histories according to a job exposure matrix. Patients had undergone general anesthesia and suffered severe head trauma more often than control subjects, but a dose-response gradient was not present. Patients reported a significantly larger number of amalgam-filled teeth before their illness than control subjects. The frequency of premature births and birth order did not differ between patients and control subjects. Patients reported significantly more relatives affected with PD than control subjects. These results support a role for environmental and genetic factors in the etiology of PD.

Semchuk KM, Love EJ. 1995. Effects of agricultural work and other proxy-derived case-control data on parkinsons-disease risk estimates. Am J Epidemiol 141(8):747-754.
Abstract: This study examined the effects on Parkinson's disease risk estimates of exposure misclassification in proxy-derived data on agricultural work, pesticide use, rural living, well water drinking, head trauma, smoking, and family history of Parkinson's disease or essential tremor. The data were collected in 1989 as part of a population-based case-control study of Parkinson's disease in Calgary, Canada. Nondemented cases (n = 130) were selected from a case register of Calgary residents with neurologist-confirmed Parkinson's disease. For each case, two matched (sex and age +/- 2.5 years) community controls were selected by random digit dialing. Forty cases and 77 controls were randomly selected as index respondents. The cases, controls, and one proxy respondent (spouse or off spring) for each index respondent were interviewed using a structured questionnaire. The data were analyzed using conditional logistic regression. Incorporation of proxy-derived data for 30% of the cases or controls, or both, resulted in considerable misclassification of exposure for some variables and, in most cases, attenuation of the odds ratio. The results indicate that pooling dichotomously classified data derived in part from self- and proxy respondents may result in biased estimates of Parkinson's disease risk associated with agricultural, family history, and head trauma factors.

Semchuk KM, Love EJ, Lee RG. 1992. Parkinsons-disease and exposure to agricultural work and pesticide chemicals. Neurology 42(7):1328-1335.
Abstract: This population-based case-control study of 130 Calgary residents with neurologist-confirmed idiopathic Parkinson's disease (PD) and 260 randomly selected age- and sex-matched community controls attempted to determine whether agricultural work or the occupational use of pesticide chemicals is associated with an increased risk for PD. We obtained by personal interviews lifetime occupational histories, including chemical exposure data, and analyzed the data using conditional logistic regression for matched sets. In the univariate analysis, a history of field crop farming, grain farming, herbicide use, or insecticide use resulted in a significantly increased crude estimate of the PD risk, and the data suggested a dose-response relation between the PD risk and the cumulative lifetime exposure to field crop farming and to grain farming. However, in the multivariate analysis, which controlled for potential

confounding or interaction between the exposure variables, previous occupational herbicide use was consistently the only significant predictor of PD risk. These results support the hypothesis that the occupational use of herbicides is associated with an increased risk for PD.

Semchuk KM, Love EJ, Lee RG. 1993. Parkinsons-disease - a test of the multifactorial etiologic hypothesis. Neurology 43(6):1173-1180. Abstract: We studied the relative etiologic importance upon the development of Parkinson's disease (PD) of occupational exposure to herbicides and other compounds, ionizing radiation exposure, family history of PD and essential tremor, smoking, and history of various viral and other medical conditions. We identified patients (n = 130) with neurologist-confirmed idiopathic PD through contacts with Calgary general hospitals, long-term care facilities, neurologists, the Movement Disorder Clinic, and the Parkinson's Society of Southern Alberta, and selected two matched (by sex and age +/- 2.5 years) community controls for each case by random digit dialing. We obtained lifetime work, chemical, radiation, medical, and smoking exposure histories and family histories of PD and essential tremor by personal interviews, and analyzed the data using conditional logistic regression for matched sets. After controlling for potential confounding and interaction between the exposure variables, using multivariate statistical methods, having a family history of PD was the strongest predictor of PD risk, followed by head trauma and then occupational herbicide use. Cases and controls did not differ in their previous exposures to smoking or ionizing radiation; family history of essential tremor; work-related contact with aluminum, carbon monoxide, cyanide, manganese, mercury, or mineral oils; or history of arteriosclerosis, chicken pox, encephalitis, hypertension, hypotension, measles, mumps, rubella, or Spanish flu. These results support the hypothesis of a multifactorial etiology for PD, probably involving genetic, environmental, trauma, and possibly other factors.

Seo BB, Nakamaru-Ogiso E, Flotte TR, Yagi T, Matsuno-Yagi A. 2002. A single-subunit NADH-Quinone oxidoreductase renders resistance to mammalian nerve cells against complex I inhibition. Molecular Therapy 6(3):336-341. Abstract: Numerous studies suggest that dysfunction of mitochondrial proton-translocating NADH-ubiquinone oxidoreductase (complex I) is associated with neurodegenerative disorders, such as Parkinson's disease and Huntington's disease. Development of methods to correct complex I defects seems important. We have previously shown that the single-subunit NADH dehydrogenase of Saccharomyces cerevisiae (Ndi1P) can work as a replacement for complex I in mammalian cells. Using a recombinant adeno-associated virus vector carrying the NDI1 gene, we now demonstrated that the Ndi1 enzyme was successfully expressed in the dopaminergic cell lines rat PC12 and mouse MN9D. The cells expressing the Ndi1 protein were resistant to known inhibitors of complex 1, such as rotenone and pyridaben. In addition, the NDI1-transduced cells were still capable of morphological maturation as examined by induction of neurite outgrowth. Also, it was possible to infect the cells after the maturation. The expressed Ndi1 protein was located both in cell bodies and in neurites and

was functionally active. It is conceivable that the NDI1 gene will be a promising tool in the treatment of neurodegenerative conditions caused by complex I inhibition.

Seth K, Agrawal AK, Aziz MH, Ahmad A, Shukla Y, Mathur N, Seth PK. 2002. Induced expression of early response genes/oxidative injury in rat pheochromocytoma (PC12) cell line by 6-hydroxydopamine: implication for Parkinson's disease. Neurosci Lett 330(1):89-93.
Abstract: The expression of early response gene proteins c-Fos, c-Jun, and GAP-43 and their association with 6-hydroxydopamine (6-OHDA)-mediated oxidative injury were investigated using catecholaminergic PC12 cell line. Significant induction in the expression of c-Fos ($P < 0.01$), c-Jun ($P < 0.001$) and GAP-43 ($P < 0.05$) was observed following 2 h exposure to 6-OHDA (10(-6) M), which persisted during 24 h of observation. The exposed cells exhibited an increase in lipid peroxidation (48, 59 and 33%) along with decreased catalase activity (49, 30 and 13%) and glutathione levels (39, 28 and 16%) following 24, 48 and 72 h exposure, respectively. A concentration-dependent functional impairment of mitochondria as studied by 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay and decreased cell survival were also observed following 6-OHDA (10(-4), 10(-5) M) exposure for 24, 48 and 72 h. The results indicate a role of the early response gene in oxidative stress-mediated dopaminergic cell death by 6-OHDA. Similar mechanisms may also be operative in the development of Parkinson's disease, as an increased presence/formation of endogenous 6-OHDA has been reported in Parkinson's patients. (C) 2002 Published by Elsevier Science Ireland Ltd.

Seyfried J, Soldner F, Kunz WS, Schulz JB, Klockgether T, Kovar KA, Wullner U. 2000. Effect of 1-methyl-4-phenylpyridinium on glutathione in rat pheochromocytoma PC 12 cells. Neurochem Int 36(6):489-497.
Abstract: We investigated the effect of the selective dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP+) on glutathione redox status and the generation of reactive oxygen intermediates (ROI) in rat pheochromocytoma PC 12 cells in vitro. Treatment with MPP+ (250 mu M) led to a 63% increase of reduced glutathione (GSH) after 24 h, while a 10-fold higher concentration of MPP+ (2.5 mM) depleted cellular GSH to 12.5% of control levels within that time. Similarly, the complex I-inhibitor rotenone induced a time-dependent loss of GSH at 1 and 10 mu M, whereas treatment with lower concentrations of rotenone (0.1, 0.01 mu M) increased cellular GSH. Both MPP+ and rotenone increased cellular levels of oxidised glutathione (GSSG) and the higher concentrations of both compounds led to an elevated ratio of oxidised glutathione (GSSG) vs total glutathione (GSH + GSSG) indicating a shift in cellular redox balance. MPP + or rotenone did not induce the generation of ROI or significant elevation of intracellular levels of thiobabituric acid reactive substances (TBARS) for up to 48 h. Our data suggest that MPP+ has differential effects on glutathione homeostasis depending on the degree of complex I-inhibition and that inhibition of complex I is not sufficient to generate ROI in this paradigm. (C) 2000 Elsevier Science Ltd. All rights reserved.

Shahar E, Andraws J. 2001. Extra-pyramidal parkinsonism complicating organophosphate insecticide poisoning. Eur J Paediatr Neurol 5(6):261-4.
Abstract: We present a 1 7-year-old female with acute extra-pyramidal parkinsonism complicating a suicidal attempt with the organophosphate insecticide chlorpyrifos, who was initially suspected to have developed severe depression or psychosis. On admission she was stupurous, with diarrhoea and massive salivation lapsing into respiratory failure and coma. Following atropine and toxogonin treatment along with mechanical ventilation she developed overt extrapyramidal parkinsonism and encephalopathy, characterized by impaired sensorium and agitation, mask facies along with a muffled voice and swallowing impairment, a resting tremor with cogwheel rigidity switching to bradykinetic choreoathetotic movements. Once a parkinsonian syndrome was diagnosed, she was given amantadine therapy with complete recovery. The patient is presently maintained on amantadine therapy; there was mild worsening of her extrapyramidal signs following unplanned discontinuation of this medication, and on follow-up assessments after 9 months she is virtually asymptomatic. A parkinsonian extrapyramidal syndrome, complicating organophosphate intoxication, should therefore also be taken into account in any patient with organophosphate poisoning, presenting with marked behavioural alterations, rigidity or akinetic mutism, and beneficial response to amantadine.

Shahar E, Bentur Y, Bar-Joseph G, Cahana A, Hershman E. 2005. Extrapyramidal Parkinsonism complicating acute organophosphate insecticide poisoning. Pediatr Neurol 33(5):378-382.
Abstract: The aim of this study is to report our experience with a child who developed extrapyramidal perturbations complicating acute organophosphate insecticides poisoning and to review the literature reporting on basal ganglia impairment associated with this poisoning. Our patient had developed overt parkinsonism presenting with a resting tremor, expressionless face, and lack of blinking along with marked cogwheel rigidity and a stooped, slow gait. He was alert, coherent, and cooperative, yet agitated. The parkinsonian perturbations developed 5 days after an accidental ingestion of a raw eggplant sprayed with the organophosphate dimethoate (Rogor) when he had already recovered from the acute cholinergic crisis, the first stage of organophosphate poisoning. Such a presentation was initially perceived by his caregivers as severe reactive depression or even psychosis. Once a parkinsonian syndrome was diagnosed, he was begun on amantadine and completely recovered within 1 week with no relapse of symptoms. Basal ganglia impairment should be considered in any patient who develops extrapyramidal symptoms such as marked rigidity and bradykinesia or choreoathetosis while recovering from the acute cholinergic phase of organophosphate insecticide poisoning. Thus, administration of a drug such as amantadine, which probably enhances neurotransmission, may hasten the rate of recovery and prevent long-term neurologic and emotional sequelae. (c) 2005 by Elsevier Inc. All rights reserved.

Shamoto-Nagai M, Maruyama W, Kato Y, Isobe K, Tanaka M, Naoi M, Osawa T.

2003. An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells. J Neurosci Res 74(4):589-597.
Abstract: In Parkinson's disease, characteristic pathological features are the cell death of nigrostriatal dopamine neurons and the formation of Lewy bodies composed of oxidized proteins. Mitochondrial dysfunction and aggregation of abnormal proteins have been proposed to cause the pathological changes. However, the relation between these two factors remains to be clarified. In this study, the effects of mitochondrial dysfunction on the oxidative modification and accumulation of proteins were analyzed using an inhibitor of mitochondrial complex I, rotenone, and antibodies against acrolein- and dityrosine-modified proteins. Under conditions inducing mainly apoptosis in neuroblastoma SH-SY5Y cells, rotenone markedly increased oxidized proteins, especially those modified with acrolein, even though the increase in intracellular reactive oxygen and nitrogen species was only transient and was not so marked. In addition, the activity of the proteasome system degrading oxidized proteins was reduced profoundly after treatment with rotenone. The 20S beta subunit of proteasome was modified with acrolein, to which other acrolein-modified proteins were found to bind, as shown by coprecipitation with the antibody against 20S beta subunit. These results suggest that mitochondrial dysfunction, especially decreased activity of complex I, may reduce proteasome activity through oxidative modification of proteasome itself and aggregation with other oxidized proteins. This mechanism might account for the accumulation of modified protein and, at least partially, for cell death of the dopamine neurons in Parkinson's disease. (C) 2003 Wiley-Liss, Inc.

Shang TS, Uihlein AV, Van Asten J, Kalyanaraman B, Hillard CJ. 2003. 1-Methyl-4-phenylpyridinium accumulates in cerebellar granule neurons via organic cation transporter 3. J Neurochem 85(2):358-367.
Abstract: 1-Methyl-4-phenylpyridinium (MPP+), the toxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, induces apoptosis in cerebellar granule neurons (CGNs). We have tested the hypothesis that organic cation transporter (OCT) 3 mediates the accumulation and, hence, the toxicity of MPP+ in CGNs. CGNs in primary culture express OCT3 but do not express mRNA for OCT1, OCT2 or the dopamine transporter. Cerebellar astrocytes are negative for OCT3 protein by immunocytochemistry. [H-3]MPP+ accumulation by CGNs exhibits first-order kinetics, and a K-t value of 5.3 +/- 1.2 mum and a T-max of 0.32 +/- 0.02 pmol per min per 10(6) cells. [H-3]MPP+ accumulation is inhibited by corticosterone, beta-estradiol and decynium 22 with K-i values of 0.25 mum, 0.17 mum and 4.0 nm respectively. [H-3]MPP+ accumulation is also inhibited by desipramine, dopamine, serotonin and norepinephrine, but is not affected by carnitine (10 mm), mazindol (9 mum) or GBR 12909 (1 mum). MPP+-induced caspase-3-like activation and cell death are prevented by pretreatment with 5 mumbeta-estradiol. In contrast, the neurotoxic effects of rotenone are unaffected by beta-estradiol. Interestingly, GBR 12909 protects CGNs from both MPP+ and rotenone

toxicity. In summary, CGNs accumulate MPP+ in manner that is consistent with uptake via OCT3 and the presence of this protein in CGNs explains their sensitivity to MPP+ toxicity.

Sharma SK, Ebadi M. 2003. Metallothionein attenuates 3-morpholinosydnonimine (SIN-1)-induced oxidative stress in dopaminergic neurons. Antioxidants & Redox Signaling 5(3):251-264.
Abstract: Parkinson's disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra. zona compacta, and in other subcortical nuclei associated with a widespread occurrence of Lewy bodies. The causes of cell death in Parkinson's disease are still poorly understood, but a defect in mitochondrial oxidative phosphorylation and enhanced oxidative stress have been proposed. We have examined 3-morpholinosydnonimine (SIN-1)-induced apoptosis in control and metallothionein-overexpressing dopaminergic neurons, with a primary objective to determine the neuroprotective potential of metallothionein against peroxynitrite-induced neurodegeneration in Parkinson's disease. SIN-I induced lipid peroxidation and triggered plasma membrane blebbing. In addition, it caused DNA fragmentation, alpha-synuclein induction, and intramitochondrial accumulation of metal ions (copper, iron, zinc, and calcium), and enhanced the synthesis of 8-hydroxy-2-deoxyguanosine. Furthermore, it down-regulated the expression of Bcl-2 and poly(ADP-ribose) polymerase, but up-regulated the expression of caspase-3 and Bax in dopaminergic (SK-N-SH) neurons. SIN-1 induced apoptosis in aging mitochondrial genome knockout cells, alpha-synuclein-transfected cells, metallothionein double-knockout cells, and caspase-3-overexpressed dopaminergic neurons. SIN-1-induced changes were attenuated with selegiline or in metallothionein-transgenic striatal fetal stem cells. SIN-1-induced oxidation of dopamine to dihydroxyphenylacetaldehyde was attenuated in metallothionein-transgenic fetal stem cells and in cells transfected with a mitochondrial genome, and enhanced in aging mitochondrial genome knockout cells, in metallothionein double-knockout cells and caspase-3 gene-overexpressing dopaminergic neurons. Selegiline, melatonin, ubiquinone, and metallothionein suppressed SIN-1-induced down-regulation of a mitochondrial genome and up-regulation of caspase-3 as determined by reverse transcription-polymerase chain reaction. The synthesis of mitochondrial 8-hydroxy-2-deoxyguanosine and apoptosis-inducing factors were increased following exposure to 1-methyl-4-phenylpyridinium ion or rotenone. Pretreatment with selegiline or metallothionein suppressed 1-methyl-4-phenylpyridinium ion-, 6-hydroxydopamine-, and rotenone-induced increases in mitochondrial 8-hydroxy-2-deoxyguanosine accumulation. Transfection of aging mitochondrial genome knockout neurons with mitochondrial genome encoding complex-1 or melanin attenuated the SIN-1-induced increase in lipid peroxidation. SIN-1 induced the expression of alpha-synuclein, caspase-3, and 8-hydroxy-2-deoxyguanosine, and augmented protein nitration. These effects were attenuated by metallothionein gene overexpression. These studies provide evidence that nitric oxide synthase activation and peroxynitrite ion overproduction may be involved in the

etiopathogenesis of Parkinson's disease, and that metallothionein gene induction may provide neuroprotection.

Shastry BS. 2001. Parkinson disease: etiology, pathogenesis and future of gene therapy. Neurosci Res 41(1):5-12.
Abstract: Parkinson disease (PD) is a progressive neurological disorder with a prevalence of 1-2% in people over the age of 50. It has a world-wide distribution and has no gender preference. The neurological hallmark of PD is the presence of Lewy bodies and is characterized by the degeneration of nigrostriatal dopaminergic neurons. The causes of PD are unknown but considerable evidence suggests a multifactorial etiology involving genetic and environmental factors. A molecular genetic approach identified three genes and at least two additional loci in rare familial forms of PD. Two of these genes are involved in the ubiquitin mediated pathway of protein degradation and the third one is a highly expressed protein in the synaptic terminal and is called alpha -synuclein. In animal models, it has been shown that use of the household pesticide which is known to contain rotenone, causes PD. Thus, a combined action of genetic and environmental factors is responsible for the pathogenesis of PD. Although use of levodopa or dopamine agonists can substantially reduce clinical symptoms, and transplantation of fetal nerve tissue still remains as an alternative therapy (although it has been recently shown to be having no overall benefit), directed delivery of glial cell derived neurotrophic factor (known to have trophic effects on dopaminergic neurons) may also be a beneficial therapeutic option for PD patients. (C) 2001 Elsevier Science Ireland Ltd and the Japan Neuroscience Society. All rights reserved.

Shavali S, Carlson EC, Swinscoe JC, Ebadi M. 2004. 1-benzyl-1,2,3,4-tetrahydroisoquinoline, a parkinsonism-inducing endogenous toxin, increases alpha-synuclein expression and causes nuclear damage in human dopaminergic cells. J Neurosci Res 76(4):563-571.
Abstract: 1-Benzyl-1,2,3,4-tetrahydroisoquinoline (1 BnTIQ), an endogenous neurotoxin, is known to cause parkinsonism in rodents and nonhuman primates. The levels of 1 BnTIQ in cerebrospinal fluid of patients with Parkinson's disease (PD) were reported to be three times higher than those in control subjects. In the present study, we have evaluated the effects of 1 BnTIQ on a-synuclein (alpha-syn) expression together with biochemical and morphological changes in human dopaminergic SH-SY5Y cells in culture. 1 BnTIQ at lower concentrations (1-50 muM) increased a-syn protein expression in a time- and dose-dependent manner in these cells. There was also up-regulation of a-syn mRNA by 1 BnTIQ. Inhibition of complex I by rotenone and depletion of glutathione by L-buthionine sulfoxamine also correlated with an increase in a-syn expression, suggesting that oxidative stress may cause an increase in a-syn levels in dopaminergic cells. Furthermore, 1 BnTIQ significantly depleted glutathione levels. 1 BnTIQ at higher concentrations (500 muM) increased reactive oxygen species levels, decreased ATP levels, and caused nuclear damage in the cells. The 1BnTIQ-induced alpha-syn upregulation was inhibited by cotreatment with the antioxidants selegiline, coenzyme Q(10), and N-acetylcystein and the caspase inhibitor DEVID-

CHO. Taken together, these results suggest that a-syn up-regulation and oxidative stress are contributing factors in 1BnTIQ-induced neurotoxicity in dopaminergic neurons in PD. (C) 2004 Wiley-Liss, Inc.

Sherer TB, Betarbet R, Greenamyre JT. 2001 May. Pathogenesis of Parkinson's disease. Curr Opin Investig Drugs 2(5):657-62.
Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by degeneration of the nigrostriatal dopaminergic pathway and the appearance of cytoplasmic proteinaceous aggregates known as Lewy bodies. Studies of familial PD have uncovered rare causative mutations in genes, including alpha-synuclein. Mutations or oxidative modification of alpha-synuclein causes it to aggregate; alpha-synuclein is a major component of the Lewy body in both familial and sporadic PD. Biochemical analysis has implicated mitochondrial dysfunction in PD. Epidemiological studies indicate a role of exposure to pesticides, some of which are mitochondrial toxins. Mitochondrial dysfunction, resulting from genetic defects, environmental toxins, or a combination of the two, may cause alpha-synuclein aggregation and produce selective neurodegeneration through mechanisms involving oxidative stress and excitotoxicity. Efforts to better define PD pathogenesis should reveal novel therapeutic targets.

Sherer TB, Betarbet R, Greenamyre JT. 2001 May 1. Pesticides and Parkinson's disease. ScientificWorldJournal 1: 207-8.
Abstract: Parkinson's disease (PD), a common neurodegenerative disorder affects approximately 1% of the population over 65. PD is a late-onset progressive motor disease characterized by tremor, rigidity (stiffness), and bradykinesia (slowness of movement). The hallmark of PD is the selective death of dopamine-containing neurons in the substantia nigra pars compacta which send their projections to the striatum and the presence of cytoplasmic aggregates called Lewy bodies. Most cases of PD are sporadic but rare cases are familial, with earlier onset. The underlying mechanisms and causes of PD still remain unclear.

Sherer TB, Betarbet R, Greenamyre JT. 2002. Environment, mitochondria, and Parkinson's disease. Neuroscientist 8(3):192-197.
Abstract: Parkinson's disease (PD) is a common and disabling neurodegenerative disease marked by progressive motor dysfunction, which results from selective degeneration of the nigrostriatal pathway. Epidemiological studies indicate that exposure to pesticides, rural living, farming, and drinking well water are associated with an increased risk of developing PD. Rare cases of PD are caused by mutations in nuclear genes, and there is increasing evidence for susceptibility genes that alter disease risk. Parkinson's disease is also associated with a systemic defect in mitochondrial complex I activity. Animal models indicate that exposure to inhibitors of mitochondrial complex 1, including pesticides, is sufficient to reproduce the features of PD, but genetic factors clearly modulate susceptibility. Complex I defects may result in oxidative stress and increase the susceptibility of neurons to excitotoxic death. In this way, environmental exposures and mitochondrial dysfunction may interact and

result in neurodegeneration.

Sherer TB, Betarbet R, Kim JH, Greenamyre JT . 2003. Selective microglial activation in the rat rotenone model of Parkinson's disease. Neurosci Lett 341(2): 87-90.
Abstract: Chronic rotenone exposure reproduces features of Parkinson's disease (PD) (Nat. Neurosci. 3 (2000) 1301; Exp. Neurol. 179 (2003) 9). We investigated the role of glial activation in rotenone toxicity in vivo. Male Lewis rats received 2-3 mg/kg rotenone per day for up to 4 weeks. In 50% of surviving rotenone-treated animals, there was nigrostriatal dopaminergic degeneration, marked by reduced tyrosine hydroxylase immunoreactivity). Extensive microglial activation, determined by OX-42-ir, occurred in striatum and nigra of rotenone-treated animals, and was prominent before anatomical evidence of dopaminergic lesions. Microglia enlarged and developed short, stubby processes in rotenone-treated animals. Rotenone-induced microglial activation was less pronounced in cortex. Reactive astrocytosis was minimal and limited to a thin rim around the lesion. Marked microglial activation with minimal astrocytosis is another pathological feature of PD reproduced by rotenone treatment. (C) 2003 Elsevier Science Ireland Ltd. All rights reserved.

Sherer TB, Betarbet R, Stout AK, Lund S, Baptista M, Panov AV, Cookson MR, Greenamyre JT. 2002. An in vitro model of Parkinson's disease: Linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage. J Neurosci 22(16):7006-7015.
Abstract: Chronic systemic complex I inhibition caused by rotenone exposure induces features of Parkinson's disease (PD) in rats, including selective nigrostriatal dopaminergic degeneration and formation of ubiquitin- and alpha-synuclein-positive inclusions (Betarbet et al., 2000). To determine underlying mechanisms of rotenone-induced cell death, we developed a chronic in vitro model based on treating human neuroblastoma cells with 5 nM rotenone for 1-4 weeks. For up to 4 weeks, cells grown in the presence of rotenone had normal morphology and growth kinetics, but at this time point, similar to5% of cells began to undergo apoptosis. Short-term rotenone treatment (1 week) elevated soluble alpha-synuclein protein levels without changing message levels, suggesting that alpha-synuclein degradation was retarded. Chronic rotenone exposure (4 weeks) increased levels of SDS-insoluble alpha-synuclein and ubiquitin. After a latency of >2 weeks, rotenone-treated cells showed evidence of oxidative stress, including loss of glutathione and increased oxidative DNA and protein damage. Chronic rotenone treatment (4 weeks) caused a slight elevation in basal apoptosis and markedly sensitized cells to further oxidative challenge. In response to H2O2, there was cytochrome c release from mitochondria, caspase-3 activation, and apoptosis, all of which occurred earlier and to a much greater extent in rotenone-treated cells; caspase inhibition provided substantial protection. These studies indicate that chronic low-grade complex I inhibition caused by rotenone exposure induces accumulation and aggregation of alpha-synuclein and ubiquitin, progressive oxidative damage, and caspase-

dependent death, mechanisms that may be central to PD pathogenesis.

Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH, Miller GW, Yagi T, Matsuno-Yagi A, Greenamyre JT. 2003. Mechanism of toxicity in rotenone models of Parkinson's disease. J Neurosci 23(34):10756-10764.
Abstract: Exposure of rats to the pesticide and complex I inhibitor rotenone reproduces features of Parkinson's disease, including selective nigrostriatal dopaminergic degeneration and alpha-synuclein-positive cytoplasmic inclusions (Betarbet et al., 2000; Sherer et al., 2003). Here, we examined mechanisms of rotenone toxicity using three model systems. In SK-N-MC human neuroblastoma cells, rotenone (10 nM to 1 muM) caused dose-dependent ATP depletion, oxidative damage, and death. To determine the molecular site of action of rotenone, cells were transfected with the rotenone-insensitive single-subunit NADH dehydrogenase of Saccharomyces cerevisiae (NDI1), which incorporates into the mammalian ETC and acts as a "replacement" for endogenous complex I. In response to rotenone, NDI1-transfected cells did not show mitochondrial impairment, oxidative damage, or death, demonstrating that these effects of rotenone were caused by specific interactions at complex I. Although rotenone caused modest ATP depletion, equivalent ATP loss induced by 2-deoxyglucose was without toxicity, arguing that bioenergetic defects were not responsible for cell death. In contrast, reducing oxidative damage with antioxidants, or by NDI1 transfection, blocked cell death. To determine the relevance of rotenone-induced oxidative damage to dopaminergic neuronal death, we used a chronic midbrain slice culture model. In this system, rotenone caused oxidative damage and dopaminergic neuronal loss, effects blocked by alpha-tocopherol. Finally, brains from rotenone-treated animals demonstrated oxidative damage, most notably in midbrain and olfactory bulb, dopaminergic regions affected by Parkinson's disease. These results, using three models of increasing complexity, demonstrate the involvement of oxidative damage in rotenone toxicity and support the evaluation of antioxidant therapies for Parkinson's disease.

Sherer TB, Kim JH, Betarbet R, Greenamyre JT . 2003. Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation. Exp Neurol 179(1):9-16.
Abstract: Previous studies demonstrated that chronic systemic exposure to the pesticide and mitochondrial toxin rotenone through jugular vein cannulation reproduced many features of Parkinson's disease (PD) in rats, including nigrostriatal dopaminergic degeneration and formation of alpha-synuclein-positive cytoplasmic inclusions in nigral neurons (R. Betarbet et aL, 2000, Nat Neurosci. 3, 1301-1306). Although novel and conceptually important, the rotenone model of PD suffered from being extremely labor-intensive. The current paper demonstrates that these same features of PD can be reproduced by chronic, systemic exposure to rotenone following implantation of subcutaneous osmotic pumps. Chronic subcutaneous exposure to low doses of rotenone (2.0-3.0 mg/kg/day) caused highly selective nigrostriatal dopaminergic lesions. Striatal neurons containing DARPP-32 (dopamine and cAMP-regulated phosphoprotein) remained intact with normal morphology, and NeuN staining revealed normal neuronal

nuclear morphology. Neurons of the globus pallidus and subthalamic nucleus were spared. Subcutaneous rotenone exposure caused alpha-synuclein-positive cytoplasmic aggregates in nigral neurons. This new protocol for chronic rotenone administration is a substantial improvement in terms of simplicity and throughput. (C) 2002 Elsevier Science (USA).

Sherer TB, Trimmer PA, Borland K, Parks JK, Bennett JP, Tuttle JB. 2001. Chronic reduction in complex I function alters calcium signaling in SH-SY5Y neuroblastoma cells. Brain Res 891(1-2):94-105.
Abstract: Sporadic, non-familial Parkinson's disease is characterized by a 15-30% reduction in complex I activity of the electron transport chain. A pharmacological model of reduced complex I activity was created by prolonged treatment of SH-SY5Y cells with low doses (5-20 nM) of rotenone, a selective inhibitor of complex I. Short-term (less than 2 week) exposure to rotenone did not influence calcium signaling, production of reactive oxygen species, or mitochondrial morphology. However, following 2 weeks of rotenone exposure, SH-SY5Y cells showed unusual calcium dynamics, specifically multiple calcium responses to carbachol, a muscarinic agonist. These secondary calcium responses were not seen in control SH-SY5Y cells and were dependent upon calcium influx. Mitochondrial membrane potential was also reduced in low dose rotenone-treated cells. These results demonstrate that a chronic, partial reduction in complex I activity, such as that seen in Parkinson's disease, can alter cell signaling events and perhaps increase the susceptibility of cells to calcium overload and subsequent cell death. (C) 2001 Elsevier Science BN. All rights reserved.

Shimazu S, Takahata K, Tamashiro A, Yoneda F, Iida Y, Saji H. 2003. Recovery of motor function and dopaminergic parameters in a mouse model of Parkinson's disease induced by co-administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and diethyldithiocarbamate. J Neural Transm 110(8):871-883.
Abstract: Diethyldithiocarbamate (DDC) enhances the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). We studied the time course of doparninergic parameters and motor function of MPTP+DDC-lesioned C57BL/6 mice, a model of Parkinson's disease. MPTP+DDC-lesioned mice showed a decrease in dopamine (DA) and its metabolites contents in their striata 1, 3 and 6 weeks after MPTP+DDC-treatment, compared with those of each control group. The partial and significant recoveries in DA, 3,4-dihydroxyphenylacetic acid, and homovanillic acid contents were also observed after 6 weeks, compared with those at 1 week after treatment. In addition, bradykinesia due to DA depletion was observed in mice 1 week after MPTP+DDC-treatment, but it was not significant 3 weeks after the treatment. L-DOPA alone and a co-administration Of L-DOPA and a monoamine oxidase-B inhibitor selegiline improved bradykinesia of this model, also suggesting that bradykinesia observed in the model was mediated to doparninergic deficiency. On the other hand, the serotonin content increased slightly but significantly after 3 or 6 weeks, suggesting compensatory activation of the serotonergic system against DA depletion. Thus, the partial recovery of doparninergic

parameters, the recovery of motor function and the compensatory activation of the serotonergic system were observed in this model 3-6 weeks after MPTP+DDC treatment.

Shimizu K, Matsubara K, Ohtaki K, Fujimaru S, Saito O, Shiono H. 2003. Paraquat induces long-lasting dopamine overflow through the excitotoxic pathway in the striatum of freely moving rats. Brain Res 976(2):243-252.
Abstract: The herbicide paraquat is an environmental factor that could be involved in the etiology of Parkinson's disease. We have previously shown that paraquat penetrates through the blood-brain barrier and is taken up by neural cells. In this study, we examined the in vivo toxic mechanism of paraquat to dopamine neurons. GBR-12909, a selective dopamine transporter inhibitor, reduced paraquat uptake into the striatal tissue including dopaminergic terminals. The subchronic treatment with systemic paraquat significantly decreased brain dopamine content in the striatum and slightly in the midbrain and cortex, and was accompanied by the diminished level of its acidic metabolites in rats. When paraquat was administered through a microdialysis probe, a transitory increase in the extracellular levels of glutamate. followed by long-lasting elevations of the extracellular levels of NOx- (NO2- plus NO3-) and dopamine were detected in the striatum of freely moving rats. This dopamine overflow lasted for more than 24 h after the paraquat treatment. Dopamine overflow was inhibited by N-G-nitro-L-arginine methyl ester, dizocilpine, 6,7-dinitroquinoxaline-2,3-dione and L-deprenyl. The toxic mechanism of paraquat involves glutamate induced activation of non-NMDA receptors, resulting in activation of NMDA receptor-channels. The influx of Ca2+ into cells stimulates nitric oxide synthase. Released NO would diffuse to dopaminergic terminals and further induce mitochondrial dysfunction by the formation of peroxynitrite, resulting in continuous and long-lasting dopamine overflow. The constant exposure to low levels of paraquat may lead to the vulnerability of dopaminergic terminals in humans, and might potentiate neurodegeneration caused by the exposure of other substances, such as endogenous dopaminergic toxins. (C) 2003 Elsevier Science B.V. All rights reserved.

Shimizu K, Matsubara K, Ohtaki K, Shiono H. 2003. Paraquat leads to dopaminergic neural vulnerability in organotypic midbrain culture. Neurosci Res 46(4):523-532.
Abstract: Paraquat (1,1'-dimethyl-4.4'-bipyridinium, PQ) is a herbicide to possibly induce Parkinson's disease (PD), since a strong correlation has been found between the incidence of the disease and the amount of PQ used. In this study, we examined PQ toxicity in rat organotypic midbrain slice cultures. PQ dose dependently reduced the number of dopaminergic neurons in cultured slices. Since this damage was prevented by GBR-12909, the dopamine transporter could be an initial step of the PQ induced dopaminergic neurotoxicity. The sequential treatments with lower PQ and 1-methyl-4-phenyl pyridinium (MPP+) doses, where each dose alone was not lethal, markedly killed dopamine neurons, suggesting that the exposure of a lower dose of PQ could lead to the vulnerability of dopaminergic neurons. This cell death was prevented by the inhibitors of

NMDA, nitric oxide synthase (NOS), cycloheximide and caspase cascade. Neurons expressing NOS were identified inside and around the regions where dopamine neurons were packed. The cell death induced by the sequential treatments with PQ and MPP+ was also rescued by L-deprenyl and dopamine D2/3 agonists. These results strongly support that the constant exposure to low levels of PQ would lead to the vulnerability of dopaminergic neurons in the nigrostriatal system by the excitotoxic pathway, and might potentiate neurodegeneration caused by the exposure of other substances and aging. (C) 2003 Elsevier Ireland Ltd and the Japan Neuroscience Society. All rights reserved.

Shimizu K, Ohtaki K, Matsubara K, Aoyama K, Uezono T, Saito O, Suno M, Ogawa K, Hayase N, Kimura K, Shiono H. 2001. Carrier-mediated processes in blood-brain barrier penetration and neural uptake of paraquat . Brain Res 906(1-2):135-142.
Abstract: Due to the structural similarity to N-methyl- 4-phenyl pyridinium (MPP+), paraquat might induce dopaminergic toxicity in the brain. However, its blood-brain barrier (BBB) penetration has not been well documented. We studied the manner of BBB penetration and neural cell uptake of paraquat using a brain microdialysis technique with HPLC/UV detection in rats. After subcutaneous administration, paraquat appeared dose-dependently in the dialysate. In contrast, MPP+ could not penetrate the BBB in either control or paraquat pre-treated rats. These data indicated that the penetration of paraquat into the brain would be mediated by a specific carrier process, not resulting from the destruction of BBB function by paraquat itself or a paraquat radical. To examine whether paraquat was carried across the BBB by a certain amino acid transporter. L-valine or L-lysine was pre-administered as a co-substrate. The pre-treatment of L-valine, which is a high affinity substrate for the neutral amino acid transporter, markedly reduced the BBB penetration of paraquat. When paraquat was administered to the striatum through a microdialysis probe, a significant amount of paraquat was detected in the striatal cells after a sequential 180-min washout with Ringer's solution. This uptake was significantly inhibited by a low Na+ condition, but not by treatment with putrescine, a potent uptake inhibitor of paraquat into lung tissue. These findings indicated that paraquat is possibly taken up into the brain by the neutral amino acid transport system, then transported into striatal, possibly neuronal, cells in a Na+-dependent manner. (C) 2001 Elsevier Science B.V. All rights reserved.

Siddhuraju P, Becker K. 2003. Studies on antioxidant activities of mucuna seed (Mucuna pruriens var utilis) extract and various non-protein amino/imino acids through in vitro models. J Sci Food Agric 83(14):1517-1524.
Abstract: The antioxidant activities of a methanolic extract of mucuna beans (Mucuna pruriens var utilis) and several non-protein amino/imino acids, namely L-3,4-dihydroxyphenylalanine (L-dopa), L-3-carboxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (compound I), (-)-1-methyl-3-carboxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (compound II) and 5-hydroxytryptophan (5-HTP), were evaluated. By virtue of their hydrogen-donating ability, all the tested compounds and the mucuna seed

extract showed excellent reducing power, with the highest values being recorded for L-dopa in a dose-dependent manner. Similarly, as compared with synthetic antioxidants (BHT and BHA) and quercetin, all the tested compounds and the seed extract were found to be more potent in free radical-scavenging activity (P < 0.05) against alpha,alpha-diphenyl-beta-picrylhydrazyl (DPPH.) radicals. Hydroxyl radicals (OH.) and superoxide anion radicals (O-2(.-)) were effectively scavenged by the tested compounds, with the exception that no scavenging activity of 5-HTP was observed on (O-2(.-)) up to a concentration of 2 mg ml(-1), as was also the case for BHA. Among the tested non-protein amino/imino acids and seed extract the highest peroxidation-inhibiting activity (95%) was recorded for S-HTP. On the other hand, in the linoleic acid/beta-carotene-bleaching system, L-dopa, compound I and compound II acted as pro-oxidants, whereas the seed extract showed only weak antioxidant activity as in the linoleic acid emulsion system. (C) 2003 Society of Chemical Industry.

Siderowf A, Stern M. 2003. Update on Parkinson disease. Ann Intern Med 138(8): 651-658.
Abstract: This Update reviews developments in the pathophysiology and treatment of Parkinson disease during the past several years. In the area of pathophysiology, studies have addressed the contribution of environmental factors such as caffeine and pesticides. Large-scale epidemiologic studies have also expanded the role genetic factors are thought to play, Detailed studies of kindreds with familial Parkinson disease due to a-synuclein and parkin have catalyzed basic science investigations into the pathologic mechanisms of the disease. These studies have led to the development of a pathophysiologic model of Parkinson disease that emphasizes abnormal protein aggregation. Studies of treatment have clarified the relative roles Of L-dopa and dopamine agonists in early Parkinson disease and shown the potential for surgical interventions, particularly deep-brain stimulation, to relieve the symptoms of advanced, medically refractory disease.

Simon N, Papa K, Vidal J, Boulamery A, Bruguerolle B. 2003. Circadian rhythms of oxidative phosphorylation: Effects of rotenone and melatonin on isolated rat brain mitochondria. Chronobiol Int 20(3):451-461.
Abstract: Mitochondrial experiments are of increasing interest in different fields of research. Inhibition of mitochondrian activities seems to play a role in Parkinson's disease and in this regard several animal models have used inhibitors of mitochondrial respiration such as rotenone or MPTP. Most of these experiments were done during the daytime. However, there is no reason for mitochondrial respiration to be constant during the 24h. This study investigated the circadian variation of oxidative phosphorylation in isolated rat brain mitochondria and the administration-time-dependent effect of rotenone and melatonin. The respiratory control ratio, state 3 and state 4, displayed a circadian fluctuation. The highest respiratory control ratio value (3.01) occurred at 04:00h, and the lowest value (2.63) at 08:00h. The highest value of state 3 and state 4 oxidative respiration occurred at 12:00h and the lowest one at 20:00h. The 24h mean decrease

in the respiratory control ratio following incubation with melatonin and rotenone was 7 and 32%, respectively; however, the exact amount of the inhibition exerted by these agents varied according to the time of the mitochondria isolation. Our results show the time of mitochondrial isolation could lead to interindividual variability. When studies require mitochondrial isolation from several animals, the time between animal experiments has to be minimized. In oxidative phosphorylation studies, the time of mitochondria isolation must be taken into account, or at least specified in the methods section.

Sindhu KM, Banerjee R, Saravanan KS, Mohanakumar KP. 2003. Involvement of apoptosis in rotenone-mediated nigral toxicity. J Neurochem 87:136.

Sindhu KM, Saravanan KS, Banerjee R, Mohanakumar KP. 2004. Reversal by antioxidants of pesticide mediated striato nigral apoptosis. J Neurochem 88:57.

Sindhu KM, Saravanan KS, Mohanakumar KP. 2005. Behavioral differences in a rotenone-induced hemiparkinsonian rat model developed following intranigral or median forebrain bundle infusion. Brain Res 1051(1-2):25-34. Abstract: A mitochondrial complex-I inhibitor, rotenone was unilaterally infused into the substantia nigra pars compacta (SNpc) or median forebrain bundle (MFB) to create hemiparkinsonian animal models and investigated spontaneous and drug-induced stereotypic rotations, as well as certain postural behaviors in Sprague-Dawley rats. Animals infused intranigrally, but not intra-MFB, with rotenone exhibited spontaneous contralateral rotations immediately after recovery from anesthesia. Head position bias and elevated body swing test showed insignificant contralateral bias in animals with nigral damage but a significant ipsilateral bias in MFB-lesioned rats. General motor activity of the animals was reduced in both the groups as indicated by reduced performance on a Plus-Maze. Intranigrally, rotenone-infused animals exhibited progressive ipsilateral rotations when challenged with d-amphetamine on the 7th, 14th, 21st, and 28th days or with apomorphine on 9th, 16th, 23rd, and 30th days. However, animals that received rotenone in MFB exhibited ipsilateral or contralateral rotations when challenged respectively with d-amphetamine or apomorphine only in the 5th week (28th and 30th days). Stereotaxic administration of rotenone into SNpc or MFB caused a significant loss of dopamine in the ipsilateral striatum (> 80% in SNpc; > 95% in MFB), when assayed employing an HPLC equipped with electrochemical detector on the 32nd day. Neuronal loss in SNpc was confirmed in coronal sections stained with cresyl violet and revealed extension of lesion towards SN pars reticulata, in SNpc-infused animals. Our results demonstrate that rotenone-induced neurodegeneration is a slow, yet progressive process similar to that in idiopathic Parkinson's disease and unlike that observed in other classical neurotoxin-mediated lesions which are abrupt and developed in few hours to days. Thus, intranigral or intra-MFB infusion of rotenone could be used for producing hemiparkinsonian animal models in rats. These findings further suggest that, while both d-amphetamine and apomorphine-induced stereotypic rotations could be used as a valuable behavioral assay

procedure to test novel drugs against Parkinson's disease, yet apomorpine-induced contralateral bias in turning is a reliable indicator of specific destruction in nigrostriatal pathway and development of postsynaptic dopamine receptor supersensitivity. (c) 2005 Elsevier B.V. All rights reserved.

Singer TP, Ramsay RR. 1990 Nov 12. Mechanism of the neurotoxicity of MPTP. An update. FEBS Lett 274(1-2):1-8.
Abstract: This review summarizes advances in our understanding of the biochemical events which underlie the remarkable neurotoxic action of MPTP (1-methyl-4-phenyl-1-1,2,3,6-tetrahydropyridine) and the parkinsonian symptoms it causes in primates. The initial biochemical event is a two-step oxidation by monoamine oxidase B in glial cells to MPP+ (1-methyl-4-phenylpyridinium). A large number of MPTP analogs substituted in the aromatic (but not in the pyridine) ring are also oxidized by monoamine oxidase A or B, is in some cases faster than any previously recognized substrate. Alkyl substitution at the 2'-position changes MPTP, a predominantly B type substrate, to an A substrate. Following concentration in the dopamine neurons by the synaptic system, which has a high affinity for the carrier, MPP+ and its positively charged neurotoxic analogs are further concentrated by the electrical gradient of the inner membrane and then more slowly penetrate the hydrophobic reaction site on NADH dehydrogenase. Both of the latter events are accelerated by the tetraphenylboron anion, which forms ion pairs with MPP+ and its analogs. Mitochondrial damage is now widely accepted as the primary cause of the MPTP induced death of the nigrostriatal cells. The molecular target of MPP +, its neurotoxic product, is NADH dehydrogenase. Recent experiments suggest that the binding site is at or near the combining site of the classical respiratory inhibitors, rotenone and piericidin A.

Singer TP, Salach JI, Castagnoli N Jr, Trevor A. 1986 May 1. Interactions of the neurotoxic amine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine with monoamine oxidases. Biochem J 235(3):785-9.
Abstract: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a thermal breakdown product of a meperidine-like narcotic used by drug abusers as a heroin substitute, produces Parkinsonian symptoms in humans and primates. The nigrostriatal toxicity is not due to MPTP itself but to one or more oxidation products resulting from the action of monoamine oxidase (MAO) on this tertiary allylamine. Both MAO A and B catalyse the oxidation of MPTP to the 1-methyl-4-phenyl-2,3-dihydropyridinium species (MPDP+), which undergoes further oxidation to the fully aromatic 1-methyl-4-phenylpyridinium species (MPP+). These bio-oxidations are blocked by selective inhibitors of MAO A and B. Additionally, MPTP, MPDP+ and MPP+ are competitive inhibitors of MAO A and B. The A form of the enzyme is particularly sensitive to this type of reversible inhibition. Both MAO A and B also are irreversibly inactivated by MPTP and MPDP+, but not by MPP+. This inactivation obeys the characteristics of a mechanism-based or 'suicide' process. The inactivation, which is accompanied by the incorporation of radioactivity from methyl-labelled MPTP, is likely to result

from covalent modification of the enzyme.

Sipos I, Tretter L, Adam-Vizi V. 2003. The production of reactive oxygen species in intact isolated nerve terminals is independent of the mitochondrial membrane potential. Neurochem Res 28(10):1575-1581.
Abstract: Dependence on mitochondrial membrane potential (DeltaPsim) of hydrogen peroxide formation of in situ mitochondria in response to inhibition of complex I or III was studied in synaptosomes. Blockage of electron flow through complex I by rotenone or that through complex III by antimycin resulted in an increase in the rate of H2O2 generation as measured with the Amplex red assay. Membrane potential of mitochondria was dissipated by either FCCP (250 nM) or DNP (50 muM) and then the rate of H2O2 production was followed. Neither of the uncouplers had a significant effect on the rate of H2O2 production induced by rotenone or antimycin. Inhibition of the F0F1-ATPase by oligomycin, which also eliminates DeltaPsim in the presence of rotenone and antimycin, respectively, was also without effect on the ROS formation induced by rotenone and only slightly reduced the antimycin-induced H2O2 production. These results indicate that ROS generation of in situ mitochondria in nerve terminals in response to inhibition of complex I or complex III is independent of DeltaPsim. In addition, we detected a significant antimycin-induced H2O2 production when the flow of electrons through complex I was inhibited by rotenone, indicating that the respiratory chain of in situ mitochondria in synaptosomes has a substantial electron influx distal from the rotenone site, which could contribute to ROS generation when the complex III is inhibited.

Sipos I, Tretter L, Adam-Vizi V. 2003. Quantitative relationship between inhibition of respiratory complexes and formation of reactive oxygen species in isolated nerve terminals. J Neurochem 84(1):112-118.
Abstract: In this study reactive oxygen species (ROS) generated in the respiratory chain were measured and the quantitative relationship between inhibition of the respiratory chain complexes and ROS formation was investigated in isolated nerve terminals. We addressed to what extent complex I, III and IV,respectively, should be inhibited to cause ROS generation. For inhibition of complex I, III and IV, rotenone, antimycin and cyanide were used, respectively, and ROS formation was followed by measuring the activity of aconitase enzyme. ROS formation was not detected until complex III was inhibited by up to 71 +/- 4%, above that threshold inhibition, decrease in aconitase activity indicated an enhanced ROS generation. Similarly, threshold inhibition of complex IV caused anaccelerated ROS production. By contrast, inactivation of complex I to a small extent (16 +/- 2%) resulted in a significant increase in ROS formation, and no clear threshold inhibition could be determined. However, the magnitude of ROS generated at complex I when it is completely inhibited is smaller than that observed when complex III or complex IV was fully inactivated. Our findings may add a novel aspect to the pathology of Parkinson's disease, showing that a moderate level of complex I inhibition characteristic in Parkinson's disease leads to significant ROS formation. The amount of ROS generated by complex I inhibition is

sufficient to inhibit in situ the activity of endogenous aconitase.

Skaper SD. 2003. Poly(Adp-Ribose) Polymerase-1 in Acute Neuronal Death and Inflammation - a Strategy for NeuroprotectionVolume 993. p 217-228. Neuroprotective Agents: Annals of the New York Academy of Sciences.
Abstract: Poly(ADP-ribose) polymerase-1 (PARP-1) is an abundant nuclear enzyme that is activated primarily by DNA damage. Upon activation, the enzyme hydrolyzes NAD(+) to nicotinamide and transfers ADP ribose units to a variety of nuclear proteins, including histories and PARP-1 itself. This process is important in facilitating DNA repair. However, excessive activation of PARP-1 can lead to significant decrements in NAD(+), and ATP depletion, and cell death (suicide hypothesis). In response to cellular damage by oxygen radicals or excitotoxicity, a rapid and strong activation of PARP-1 occurs in neurons. Excessive PARP-1 activation is implicated in a variety of insults, including cerebral and cardiac ischemia, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism, traumatic spinal cord injury, and streptozotocin-induced diabetes. The use of PARP inhibitors has, therefore, been proposed as a protective therapy in decreasing excitotoxic neuronal cell death, as,well as ischemic and other tissue damage. Excitotoxic brain lesions initially result in the primary destruction of brain parenchyma and subsequently in secondary damage of neighboring neurons hours after the insult. This secondary damage of initially surviving neurons accounts for most of the volume of the infarcted area and the loss of brain function after a stroke. One major component of secondary neuronal damage is the migration of macrophages and microglial cells toward the sites of injury, where they produce large quantities of toxic cytokines and oxygen radicals. Recent evidence indicates that this microglial migration is strongly controlled in living brain tissue by expression of the integrin CD11a, which is regulated in turn by PARP-1, proposing that PARP-1 downregulation may, therefore, be a promising strategy in protecting neurons from this secondary damage, as well. Studies demonstrating an important role for PARP-1 in the regulation of gene transcription have further increased the intricacy of poly(ADP-ribosyl)ation in the control of cell homeostasis and challenge the notion that energy collapse is the sole mechanism by which poly(ADP-ribose) formation contributes to cell death. The hypothesis that PARI's might regulate cell fate as essential modulators of death and survival transcriptional programs is discussed with relation to nuclear factor kappaB and p53.

Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. 1998. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy . Neurotoxicology 19(4-5):709-712.
Abstract: A questionnaire-based case-control study was carried out on 86 patients with neurologist-confirmed idiopathic Parkinson's disease (PD) and 86 controls similar in sex and age. The control group was recruited in outpatient specialist centers of the same University Hospital (glaucoma, psoriasis vulgaris, essential arterial hypertension and renal diseases). Exposure was defined as occupational or residential contact with a given

factor for at least IO consecutive years prior to the onset of PD. Smoking habits were defined by exclusion of those subjects who never smoked. The following risk factors were identified: cranial trauma (OR: 2.88; 95% CI: 0.98-8.49), well water use (OR: 2.78; 95% CI: 1.46-5.28) and occupational exposure to industrial chemicals (OR: 2.13; 95% CI: 1.16-3.91). Among industrial chemicals, only organic solvents were identified as significant risk factors for PD (O.R. :2.78, 95% C.I. : 7.23-6.26). Whereas no exposure to neurotoxic metals occurred among controls, making the assessment of the O.R. impossible, exposure pesticides and herbicides was similar in the two groups (O.R. : 1.15; 95% C.I. :0.56-2-36). Smoking habits was negatively associated with PD (OR: 0.41; 95% CI: 0.22-0.75), confirming the "protective" role of tobacco smoking suggested by many studies. As a whole, these results support the role of environmental factors in the etiology of PD. (C) 1998 Inter Press, Inc.

Smith MT, Ekstrom G, Sandy MS, Di Monte D. 1987 Feb 23. Studies on the mechanism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine cytotoxicity in isolated hepatocytes. Life Sci 40(8):741-8.
Abstract: Oxidative stress and covalent binding have been proposed as possible mechanisms involved in the cytotoxic effects of the parkinsonism-causing compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). However, the toxicity induced by MPTP in isolated rat hepatocytes seems to be relatively independent of oxygen radical-induced oxidative stress. Here we demonstrate that MPTP cytotoxicity is not potentiated by pretreatment with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), an inhibitor of glutathione reductase, nor prevented by the antioxidant N,N'-diphenyl-p-phenylenediamine (DPPD) or the iron-chelating agent desferrioxamine. Moreover, preincubation of hepatocytes with diethylmaleate to lower the level of intracellular reduced glutathione (to 20% of the initial value) did not affect either the rate or extent of MPTP cytotoxicity. Thus, nucleophilic soluble thiols do not seem to play a protective role against MPTP-induced cell damage, in contrast to what one would have expected if covalent protein binding and oxidative stress were involved as toxic mechanisms. On the other hand, MPTP cytotoxicity was potentiated by pretreatment of hepatocytes with cytochrome P-450 inhibitors (e.g., SKF 525A and metyrapone) and a more rapid depletion of ATP was observed in these experimental conditions. We conclude that mitochondrial damage and subsequent ATP depletion are likely to play a critical role in the toxicity of MPTP to isolated hepatocytes and that the metabolism of MPTP via the cytochrome P-450 monooxygenase system can be considered to be a detoxifying pathway.

Snyder H, Wolozin B. 2004. Pathological proteins in Parkinson's disease: focus on the proteasome. J Mol Neurosci 24(3):425-442.
Abstract: Parkinson's disease (PD) is a multifactorial disease that appears to arise from the effects of both genetic and environmental influences. Pesticides and heavy metals are the principle environmental factors that appear to impact on PD. The known genetic factors include multiple genes that have been identified in related parkinsonian syndromes, as well as alpha-synuclein. Genes associated with either PD or Parkinson-related

disorders include parkin, DJ-1, ubiquitin C-terminal hydrolase isozyme L1 (UCH-L1), nuclear receptor-related factor 1, and alpha-synuclein. alpha-Synuclein is particularly notable because it aggregates readily and is the main component of Lewy bodies (LBs). Aggregated alpha-synuclein binds the proteasome and potently inhibits proteasomal activity. Because ubiquitin accumulates in LBs, and parkin and UCH-L1 also interact with the ubiquitin proteasomal system, proteasomal dysfunction is thought to contribute to the pathophysiology of PD. Increasing numbers of experiments suggest that neurotoxins might interact with alpha-synuclein or other Parkinson-related proteins to contribute to the pathophysiology of PD. Transgenic animal models overexpressing alpha-synuclein develop age-dependent motor dysfunction and inclusions in the brain stem that contain alpha-synuclein. These models are very helpful in elucidating the pathophysiology of PD but do not completely recapitulate the disease process. The relationship between these transgenic models and PD is a subject of intense investigation.

Snyder JW, Alexander GM, Ferraro TN, Grothusen JR, Farber JL. 1993. N-methyl-4-phenylpyridinium (mpp+) potentiates the killing of cultured-hepatocytes by catecholamines. Chem Biol Interact 88(2-3):209-223.
Abstract: The role of catecholamines in the toxicity of MPTP (N-methyl-4-pheny-1,2,3,6-tetrahydropyridine) was explored. The killing of cultured hepatocytes by dopamine and 6-hydroxydopamine was enhanced following inhibition of glutathione reductase by 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), a manipulation known to sensitize such cells to an oxidative stress. The participation of activated oxygen species in the cell injury under such circumstances was shown by the ability of catalase and the ferric iron chelator deferoxamine to protect the hepatocytes. The toxicity of catecholamines was also potentiated by the mitochondrial site I (NADH dehydrogenase) inhibitor rotenone. MPP+ (N-methyl-4-phenylpyridinium), the putative toxic metabolite of MPTP is also a site I inhibitor. Incubation of hepatocytes with MPP+ similarly potentiated the toxicity of 6-hydroxydopamine, dopamine, and norepinephrine under conditions where MPP+ alone or catecholamines alone did not kill cells. Hepatocytes that had accumulated dopamine from the medium were killed by a subsequent exposure to MPP+ in the absence of a catecholamine in the medium. Hepatocytes that had not been pretreated with dopamine were not affected by the subsequent exposure to MPP+. These data indicated that catecholamines render hepatocytes more susceptible to the toxicity of MPP + and suggest that the presence of catecholamines in specific neurons in the brain may be related to the selective neurotoxicity of MPTP.

Soleo L, Defazio G, Scarselli R, Zefferino R, Livrea P, Foa V. 1996. Toxicity of fungicides containing ethylene-bis-dithiocarbamate in serumless dissociated mesencephalic-striatal primary coculture. Arch Toxicol 70(10): 678-682.
Abstract: Agricultural exposure to the organomanganese fungicide MANEB (manganese-ethylene-bis-dithiocarbamate) may induce an extrapyramidal syndrome resembling parkinsonism. To evaluate the relative role of manganese (Mn) and ethylene-bis-dithiocarbamate (EBDTC) in the hazard

of organomanganese fungicides, we studied the effects of MANCOZEB (Mn-Zinc-EBDTC) and ZINEB (Zinc-EBDTC) on serumless dissociated mesencephalic-striatal primary coculture. High affinity H-3-dopamine (DA) and C-14 GABA uptakes as well as immunocytochemical staining of tyrosine hydroxylase (TH)-containing cells were used as specific functional markers of DA and GABA neuron viability. Both MANCOZEB and ZINEB, at 10 and 50 mu M concentrations, dose dependently reduced DA and GABA viability parameters. These data suggest that EBDTC rather than Mn may be primarily responsible for the cytotoxicity of organomanganese fungicides on neuronal systems relevant to the pathophysiology of parkinsonism.

Sousa SC, Castilho RF. 2005. Protective effect of melatonin on rotenone plus Ca2+-induced mitochondrial oxidative stress and PC12 cell death. Antioxidants & Redox Signaling 7(9-10):1110-1116.
Abstract: Chronic systemic inhibition of mitochondrial respiratory chain complex I by rotenone causes nigrostriatal dopaminergic degeneration in rats, producing an in vivo experimental model of Parkinson's disease. We recently showed that micromolar Ca2+ concentrations strongly stimulate the release of reactive oxygen species in rotenone-treated isolated rat brain mitochondria. In the present work, we show that the natural antioxidant melatonin inhibits Ca2+ plus rotenone-induced oxidative stress in isolated rat brain mitochondria. In addition, the Ca2+ ionophore A23187 strongly potentiates rotenone-induced death of intact cultured pheochromocytoma (PC12) cells, in a mechanism sensitive to melatonin. Moreover, melatonin inhibits the detection of reactive oxygen species release in PC 12 cells treated with rotenone plus A23187. Melatonin does not alter free Ca2+ concentrations or the inhibitory effect of rotenone on mitochondrial complex I. We conclude that micromolar Ca2+ concentrations stimulate neuronal cell death induced by mitochondrial complex I inhibition in a mechanism involving oxidative stress, preventable by the antioxidant melatonin.

Sousa SC, Maciel EN, Vercesi AE, Castilho RF . 2003. Ca2+-induced oxidative stress in brain mitochondria treated with the respiratory chain inhibitor rotenone. FEBS Lett 543(1-3):179-183.
Abstract: In this study we show that micromolar Ca2+ concentrations (> 10 muM) strongly stimulate the release of reactive oxygen species (ROS) in rotenone-treated isolated rat forebrain mitochondria. Ca2+-stimulated mitochondrial ROS release was associated with membrane lipid peroxidation and was directly correlated with the degree of complex I inhibition by rotenone. On the other hand, Ca2+ did not increase mitochondrial ROS release in the presence of the complex I inhibitor 1-methyl-4-phenylpyridinium. Cyclosporin A had no effect on Ca2+-stimulated mitochondrial ROS release in the presence of rotenone, indicating that mitochondrial permeability transition is not involved in this process. We hypothesized that Ca2+-induced mitochondrial oxidative stress associated with partial inhibition of complex I may be an important factor in neuronal cell death observed in the neurodegenerative disorder Parkinson's disease. (C) 2003 Published by Elsevier Science B.V. on behalf

of the Federation of European Biochemical Societies.

Speciale SG. 2002. MPTP - Insights into parkinsonian neurodegeneration. Neurotoxicol Teratol 24(5):607-620.
Abstract: MPTP burst upon the medical landscape two decades ago, first as a mysterious parkinsonian epidemic, triggering an unparalleled quest for the toxin's identity, and closely followed by an intense pursuit of its cellular mechanisms of action. MPTP treatment created an animal model of many features of Parkinson's disease (PD), used primarily in primates and later in mice. The critical role of oxidative stress damage to vulnerable dopamine neurons, as well as for neurodegenerative diseases in general, emerged from MPTP neurotoxicity. A remarkable cross-fertilization of basic and clinical findings, including genetic and epidemiologic studies, has greatly advanced our understanding of PD and revealed multiple factors contributing to the parkinsonian phenotypes. Brain imaging localizes sites of action and provides potential presymptomatic diagnostic testing. Epidemiologic reports linking PD with pesticide exposure were complimented by supportive evidence from biochemical studies of MPTP and structurally related compounds, especially after low-level, long-term exposure. Genetic studies on the role of risk genes, such as alpha-synuclein or parkin, have been validated by biochemical, anatomical and neurochemical investigations showing factors interacting to produce pathophysiology in the animal model. Focusing on the pivotal role of mitochondria, subcellular pathways participating in cell death have been clarified by unraveling similar sites of action of MPTP. Along the way, compounds antagonizing or potentiating MPTP effects indicated new PD therapies, some of the former achieving clinical trials. The future is encouraging for combating PD and will continue to benefit from the MPTP neurotoxicity model. (C) 2002 Elsevier Science Inc. All rights reserved.

Sperlagh B, Milusheva E, Baranyi M, Kittel A, Vizi ES. 2005. Dysregulation of striatal neurotransmitter release in the rotenone model of Parkinson's disease. J Neurochem 94:120.

Starkov AA, Fiskum G, Chinopoulos C, Lorenzo BJ, Browne SE, Patel MS, Beal MF. 2004. Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species. J Neurosci 24(36):7779-7788.
Abstract: Mitochondria-produced reactive oxygen species (ROS) are thought to contribute to cell death caused by a multitude of pathological conditions. The molecular sites of mitochondrial ROS production are not well established but are generally thought to be located in complex I and complex III of the electron transport chain. We measured H2O2 production, respiration, and NADPH reduction level in rat brain mitochondria oxidizing a variety of respiratory substrates. Under conditions of maximum respiration induced with either ADP or carbonyl cyanide p-trifluoromethoxyphenylhydrazone, alpha-ketoglutarate supported the highest rate of H2O2 production. In the absence of ADP or in the presence of rotenone, H2O2 production rates correlated with the reduction level of mitochondrial NADPH with various substrates, with the exception of alpha-ketoglutarate. Isolated mitochondrial alpha-ketoglutarate dehydrogenase

(KGDHC) and pyruvate dehydrogenase (PDHC) complexes produced superoxide and H2O2. NAD(+) inhibited ROS production by the isolated enzymes and by permeabilized mitochondria. We also measured H2O2 production by brain mitochondria isolated from heterozygous knock-out mice deficient in dihydrolipoyl dehydrogenase (Dld). Although this enzyme is a part of both KGDHC and PDHC, there was greater impairment of KGDHC activity in Dld-deficient mitochondria. These mitochondria also produced significantly less H2O2 than mitochondria isolated from their littermate wild-type mice. The data strongly indicate that KGDHC is a primary site of ROS production in normally functioning mitochondria.

Starkov AA, Polster BM, Fiskum G. 2002. Regulation of hydrogen peroxide production by brain mitochondria by calcium and Bax. J Neurochem 83(1): 220-228.
Abstract: Abnormal accumulation of Ca2+ and exposure to pro-apoptotic proteins, such as Bax, is believed to stimulate mitochondrial generation of reactive oxygen species (ROS) and contribute to neural cell death during acute ischemic and traumatic brain injury, and in neurodegenerative diseases, e.g. Parkinson's disease. However, the mechanism by which Ca2 + or apoptotic proteins stimulate mitochondrial ROS production is unclear. We used a sensitive fluorescent probe to compare the effects of Ca2+ on H-2 O-2 emission by isolated rat brain mitochondria in the presence of physiological concentrations of ATP and Mg2+ and different respiratory substrates. In the absence of respiratory chain inhibitors, Ca2+ suppressed H-2 O-2 generation and reduced the membrane potential of mitochondria oxidizing succinate, or glutamate plus malate. In the presence of the respiratory chain Complex I inhibitor rotenone, accumulation of Ca2+ stimulated H-2 O-2 production by mitochondria oxidizing succinate, and this stimulation was associated with release of mitochondrial cytochrome c . In the presence of glutamate plus malate, or succinate, cytochrome c release and H-2 O-2 formation were stimulated by human recombinant full-length Bax in the presence of a BH3 cell death domain peptide. These results indicate that in the presence of ATP and Mg2+ , Ca2+ accumulation either inhibits or stimulates mitochondrial H-2 O-2 production, depending on the respiratory substrate and the effect of Ca2+ on the mitochondrial membrane potential. Bax plus a BH3 domain peptide stimulate H-2 O-2 production by brain mitochondria due to release of cytochrome c and this stimulation is insensitive to changes in membrane potential.

Stasch JP, Russ H, Schacht U, Witteler M, Neuser D, Gerlach M, Leven M, Kuhn W, Jutzi P, Przuntek H. 1988 Aug. 4,4-Diphenylpiperidine derivates and their sila analogues. A comparative study of their interaction with neural receptor biding sites and synaptosomal monoamine uptake. Arzneimittelforschung 38(8):1075-8.
Abstract: The potential anti-Parkinson drugs 1-R-4,4-diphenylpiperidines and 1-R-4,4-diphenyl-4-sila-piperidines (R = H, CH3, i-propyl and t-butyl) were evaluated for their neuroreceptor affinity with respect to their structure-activity relationship. In these compounds substitution of the central carbon at position 4 by a silicon leads to more lipophilic substances. While the binding of these compounds to dopamine, serotonin and gamma-

aminobutyric acid/benzodiazepine receptors is relatively non-specific, the binding to the mu- and delta-subtypes of opiate receptors and to the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine receptor binding site show probably pharmacologically relevant effects. In almost all cases the sila-compounds have a slightly higher receptor affinity than the corresponding carbon-compounds. The studies on the uptake sites for the biogenic amines noradrenaline, dopamine and serotonin, on the other hand, reveal some considerable differences between the carbon- and silicon-containing analogues. The 4,4-diphenyl-4-sila-piperidine has much stronger uptake inhibiting properties for noradrenaline and serotonin than the corresponding carbon compound.

Stedeford T, Cardozo-Pelaez F, Nemeth N, Song SJ, Harbison RD, Sanchez-Ramos J. 2001. Comparison of base-excision repair capacity in proliferating and differentiated PC 12 cells following acute challenge with dieldrin. Free Radic Biol Med 31(10):1272-1278.
Abstract: Dieldrin, an organochlorine pesticide and known neurotoxicant, is ubiquitously distributed in the environment. Dieldrin depletes brain monoamines in some animal species and is toxic for dopaminergic neurons in vitro. Dieldrin interferes with mitochondrial electron transport and increases generation of superoxide anion. Reactive oxygen species have been shown to produce oxidative lesions to DNA bases, i.e., 8-hydroxy-2'-deoxyguanosine (8-oxodGuo). Accumulation of 8-oxodGuo has been shown to be promutagenic in proliferating cells, and can lead to degeneration in fully differentiated cells. The objective of this study was to determine the effects of dieldrin exposure on the activity of the enzyme responsible for removing 8-oxodGuo, OGG1, from undifferentiated (untreated with NGF) and differentiated (NGF-treated) PC12 cells. Proliferating PC 12 cells exhibited a mild upregulation of glycosylase activity, reaching a maximum by 1 h and returning to baseline by 6 h. Differentiated (+) NGF cells showed a time-dependent decline in activity reaching a nadir at 3 h with a return towards baseline by 6 h. Levels of the damaged base, 8-oxodGuo, in the differentiated PC12 cells appeared to be regulated by the activity of OGG1, In contrast, levels of the damaged base in actively proliferating cells were independent of the OGG1 activity. This difference between actively dividing and differentiated cells in the regulation of base-excision repair and DNA damage accumulation explains, in part, the vulnerability of postmitotic neurons to oxidative stresses and neurotoxins. (C) 2001 Elsevier Science Inc.

Stephans SE, Miller GW, Levey AI, Greenamyre JT. 2002. Acute mitochondrial and chronic toxicological effects of 1-methyl-4-phenylpyridinium in human neuroblastoma cells. Neurotoxicology 23(4-5):569-580.
Abstract: At low micromolar concentrations, 1-methyl-4-phenylpyridinium (MPP+), the toxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) selectively kills nigrostriatal dopaminergic neurons by mechanisms believed to involve impairment of mitochondrial complex I. A human neuroblastoma cell line expressing the dopamine transporter (DAT) was utilized to examine the effects of MPP+ on acute physiologic responses and subsequent cell death. Acute responses were

measured by microphysiometry and by monitoring mitochondrial membrane potential with [H-3]tetraphenylphosphonium (TPP+) uptake. MPP+ (10 muM) increased extracellular proton excretion in DAT-expressing cells within 2-3 min, but had no effect in untransfected cells. The lipophilic complex I inhibitor rotenone, increased proton excretion in both cell lines. In DAT-expressing cells, mitochondrial membrane potential was reduced within I h of 10 muM MPP+ exposure. Rotenone reduced mitochondrial membrane potential in both cell lines. MPP+ caused apoptotic death of DAT-transfected cells 2-3 days after drug application, but did not kill untransfected cells. Thus, MPP+ produces immediate mitochondrial impairment only in cells that express DAT and these changes occur days before overt cellular toxicity. The magnitude, time course and nature of these changes were similar to those produced by rotenone, confirming the site of action of MPP+ as mitochondrial complex L These immediate mitochondrial effects appear to be an accurate predictor of subsequent cell death. (C) 2002 Elsevier Science Inc. All rights reserved.

Stephenson J. 2000. Exposure to home pesticides linked to Parkinson disease. Jama-Journal of the American Medical Association 283(23):3055-3056.

Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, Gollomp S, Stolley P. 1991 . The epidemiology of parkinsons-disease - a case-control study of young-onset and old-onset patients. Arch Neurol 48(9):903-907. Abstract: While the cause of Parkinson's disease (PD) remains unknown, recent evidence suggests that certain external factors, ie, environmental agents, may act as neurotoxins, initiating the chain of oxidative reactions that ultimately destroy neurons in the substantia nigra. Young-onset PD might result from greater exposure to a putative neurotoxin. This hypothesis has rekindled interest in the epidemiology of PD. We therefore conducted a detailed analysis of various environmental exposures and early life experiences in 80 patients with old-onset PD (at an age older than 60 years), 69 young-onset patients (younger than 40 years), and 149 age- and sex-matched control subjects. Contrary to previous reports, we were unable to implicate well water or exposure to herbicides, pesticides, or industrial toxins as significant PD risk factors. A residential history of rural living was reported by more patient cases than control subjects and was marginally significant. On the other hand, at least one episode of head trauma "severe enough to cause vertigo, dizziness, blurred or double vision, seizures or convulsions, transient memory loss, personality changes, or paralysis" occurred significantly more often prior to disease onset in patients with both young-onset and old-onset PD than in control subjects (odds ratio = 2.7). When adjusted for head trauma and rural living, smoking was inversely associated with PD, as has been previously reported (odds ratio = 0.5). There were no significant differences in early life experiences or environmental exposures between young-onset and old-onset patients. We suggest that the risk of developing PD is influenced by a variety of factors. While we were unable to link specific environmental agents with PD, our study suggests that head trauma should be reassessed as a potential risk factor for PD.

Steyn SJ, Mienie LJ, Van Der Schyf CJ. 2000. beta-Oxidation of [9,10(n)-H-3] palmitate by human leukocytes: A simple in situ assay to assess mitochondrial toxicity in the presence of toxins. Toxicology Methods 10(2): 99-109.
Abstract: We utilized the beta-oxidation of [9,10(n)-H-3]palmitate in human leukocytes as a. simple assay to assess mitochondrial toxicity. Advantages of the use of tritiated fatty acids in lieu of C-14-labeled fatty acids include less interassay variation, higher specific activities obtained at a lower cost, and the relatively small number of cells required. In our assay, only 50 mu g cellular protein (approximate to 5 x 10(4) leukocytes) are required per beta-oxidation reaction as opposed to 1 x 10(6) Leukocytes required in the beta-oxidation reaction with C-14-labeled fatty acids. The higher specific activities obtained substantially reduced assay volumes, and 96 well microtiter plates could be used to conduct the assays. Rotenone (a mitochondrial complex I inhibitor) and antimycin (a mitochondrial complex III inhibitor) acutely inhibited the beta-oxidation of [9,10(n)-H-3]palmitate, thereby validating our assay. This assay offers an in situ or even a pseudo in vivo rendering of mitochondrial inhibition while potential effects of the cell membrane or cytosol or both on the toxicology of the compounds are simultaneously taken into account. We exploited these properties of our assay to investigate the in. situ mitochondrial inhibitory properties of the Parkinsonian-inducing drug MPTP and its neurotoxic pyridinium metabolite, MPP+.

Sturgess NC, Foster AJ, Marks L. 2004. Lack of effect of paraquat on the nigrostriatal dopaminergic system of the rat and mouse. Neurotoxicology 25(4): 719.

Sun F, Anantharam V, Latchoumycandane C, Kanthasamy A, Kanthasamy AG. 2005. Dieldrin induces ubiquitin-proteasome dysfunction in alpha-synuclein overexpressing dopaminergic neuronal cells and enhances susceptibility to apoptotic cell death. J Pharmacol Exp Ther 315(1):69-79.
Abstract: Exposure to pesticides is implicated in the etiopathogenesis of Parkinson's disease (PD). The organochlorine pesticide dieldrin is one of the environmental chemicals potentially linked to PD. Because recent evidence indicates that abnormal accumulation and aggregation of alpha-synuclein and ubiquitin-proteasome system dysfunction can contribute to the degenerative processes of PD, in the present study we examined whether the environmental pesticide dieldrin impairs proteasomal function and subsequently promotes apoptotic cell death in rat mesencephalic dopaminergic neuronal cells overexpressing human alpha-synuclein. Overexpression of wild-type alpha-synuclein significantly reduced the proteasomal activity. Dieldrin exposure dose-dependently (0-70 mu M) decreased proteasomal activity, and 30 mu M dieldrin inhibited activity by more than 60% in alpha-synuclein cells. Confocal microscopic analysis of dieldrin-treated alpha-synuclein cells revealed that alpha-synuclein-positive protein aggregates colocalized with ubiquitin protein. Further characterization of the aggregates with the autophagosomal marker mondansyl cadaverine and the lysosomal marker and dot-blot analysis revealed that these protein oligomeric aggregates were distinct from

autophagosomes and lysosomes. The dieldrin-induced proteasomal dysfunction in alpha-synuclein cells was also confirmed by significant accumulation of ubiquitin protein conjugates in the detergent-insoluble fraction. We found that proteasomal inhibition preceded cell death after dieldrin treatment and that alpha-synuclein cells were more sensitive than vector cells to the toxicity. Furthermore, measurement of caspase-3 and DNA fragmentation confirmed the enhanced sensitivity of alpha-synuclein cells to dieldrin-induced apoptosis. Together, our results suggest that increased expression of alpha-synuclein predisposes dopaminergic cells to proteasomal dysfunction, which can be further exacerbated by environmental exposure to certain neurotoxic compounds, such as dieldrin.

Tada-Oikawa S, Hiraku Y, Kawanishi M, Kawanishi S. 2003. Mechanism for generation of hydrogen peroxide and change of mitochondrial membrane potential during rotenone-induced apoptosis. Life Sci 73(25):3277-3288.
Abstract: Rotenone, an inhibitor of NADH dehydrogenase complex, is a naturally occurring insecticide, which is capable of inducing apoptosis. Rotenone-induced apoptosis is considered to contribute to its anticancer effect and the etiology of Parkinson's disease (PD). We demonstrated that rotenone induced internucleosomal DNA fragmentation, DNA ladder formation, in human cultured cells, HL-60 (promyelocytic leukemia) and BJAB cells (B-cell lymphoma). Flow cytometry showed that rotenone induced H2O2 generation, followed by significant changes in the mitochondrial membrane potential (DeltaPsim). Caspase-3 activity increased in HL-60 cells in a time-dependent manner. These apoptotic events were delayed in HP100 cells, an H2O2-resistant clone of HL-60, confirming the involvement of H2O2 in apoptosis. Expression of anti-apoptotic protein, Bcl-2, in BJAB cells drastically inhibited DeltaPsim change and DNA ladder formation but not H2O2 generation, confirming the participation of mitochondrial dysfunction in apoptosis. NAD(P)H oxidase inhibitors prevented H2O2 generation and DNA ladder formation. These results suggest that rotenone induces O-2(-)-derived H2O2 generation through inhibition of NADH dehydrogenase complex and/or activation of NAD(P)H oxidase, and H2O2 generation causes the disruption of mitochondrial membrane in rotenone-induced apoptosis. (C) 2003 Elsevier Inc. All rights reserved.

Tafur AJ, Gonzalez L, Idrovo LA, Tafur A. 2005. Unusual complication of an organophosphate poisoning. Emergency Medicine Journal 22(7):531.

Tai KK, Mccrossan ZA, Abbott GW. 2003. Activation of mitochondrial ATP-sensitive potassium channels increases cell viability against rotenone-induced cell death. J Neurochem 84(5):1193-1200.
Abstract: We recently showed that activation of ATP-sensitive potassium (K-ATP) channels in PC12 cells induces protection against the neurotoxic effect of rotenone, a mitochondrial complex I inhibitor. In this study, we sought to determine the locus of the K-ATP channels that mediate this protection in PC12 cells. We found that pretreatment of PC12 cells with diazoxide, a mitochondrial K-ATP channel selective opener, dose-dependently increases cell viability against rotenone-induced cell death as

indicated in trypan blue exclusion assays. The protective effect of this preconditioning is attenuated by 5-hydroxydecanoic acid (5-HD), a selective mitochondrial K-ATP channel antagonist but not in the presence of HMR-1098, a selective plasma membrane K-ATP potassium channel antagonist. In contrast, P-1075, a selective plasma membrane K-ATP channel opener, does not induce protection. Using specific antibodies against SUR1 and Kir6.1, we detected immunoreactive proteins of apparent molecular masses 155 and 50 kDa, corresponding to those previously reported for SUR1 and Kir6.1, respectively, in the mitochondria-enriched fraction of PC12 cells. In addition, whole cell patch-clamp studies revealed that inward currents in PC12 cells are insensitive to P-1075, HMR-1098, glibenclamide and diazoxide, indicating that functional plasma membrane K-ATP channels are negligible. Taken together, our results demonstrate for the first time that activation of mitochondrial K-ATP channels elicits protection against rotenone-induced cell death.

Tai KK, Truong DD. 2002. Activation of adenosine triphosphate-sensitive potassium channels confers protection against rotenone-induced cell death: Therapeutic implications for Parkinson's disease. J Neurosci Res 69(4): 559-566.
Abstract: It is anticipated that further understanding of the protective mechanism induced by ischemic preconditioning will improve prognosis for patients of ischemic injury. It is not known whether preconditioning exerts beneficial actions in neurodegenerative diseases, in which ischemic injury plays a causative role. Here we show that transient activation of ATP-sensitive potassium channels, a trigger in ischemic preconditioning signaling, confers protection in PC12 cells and SH-SY5Y cells against neurotoxic effect of rotenone and MPTP, mitochondrial complex I inhibitors that have been implicated in the pathogenesis of Parkinson's disease. The degree of protection is in proportion to the bouts of exposure to an ATP-sensitive potassium channel opener, a feature reminiscent of ischemic tolerance in vivo. Protection is sensitive to a protein synthesis inhibitor, indicating the involvement of de novo protein synthesis in the protective processes. Pretreatment of PC12 cells with preconditioning stimuli FeSO4 or xanthine/xanthine oxidase also confers protection against rotenone-induced cell death. Our results demonstrate for the first time the protective role of ATP-sensitive potassium channels in a dopaminergic neuronal cell line against rotenone-induced neurotoxicity and conceptually support the view that ischemic preconditioning-derived therapeutic strategies may have potential and feasibility in therapy for Parkinson's disease. (C) 2002 Wiley-Liss, Inc.

Takahata K, Shimazu S, Yoneda F, Ogawa M, Iida Y, Saji H. 2003. Effects of monoamine oxidase inhibitors on the diethyldithiocarbamate-induced enhancement of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in C57BL/6 mice. J Neural Transm 110(8):859-869.
Abstract: Diethyldithiocarbamate (DDC) is known to potentiate the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The aims of the present study were to provide biochemical, pathological and behavioral evidence for the degeneration of dopamine (DA) neurons in

C57BL/6 strain mice treated simultaneously with DDC and MPTP, and to evaluate the effects of monoamine oxidase (MAO) inhibitors on DDC-enhanced MPTP toxicity. DDC (400 mg/kg)+MPTP (30 mg/kg) treatment decreased significantly the levels of striatal DA and its metabolites and induced bradykinesia. In mice treated with DDC+MPTP, degenerative areas were found in striatum, substantia nigra and tuberculum olfactorium by assessment of the binding of [I-125] RTI-121, a DA transporter ligand. Pretreatment with a MAO-B inhibitor selegiline prior to the administration of DDC and MPTP completely inhibited the decrease in the levels of DA and its metabolites, bradykinesia and degeneration of dopaminergic nerve terminals. In contrast, the protective action of clorgyline was not clearly observed in this model system.

Takeshige K. 1994 Dec. [Superoxide formation and lipid peroxidation by the mitochondrial electron-transfer chain]. Rinsho Shinkeigaku 34(12): 1269-71.
Abstract: Isolated mitochondria supplemented with succinate or NAD(+)-linked substrates generate hydrogen peroxide (H2O2) in State 4 and the generation is enhanced by antimycin A, an inhibitor of the respiratory chain. Superoxide is a stoichiometric precursor of mitochondrial H2O2 because the ratio of O2-/H2O2 generation rates is close to 2.0 and is generated by an autoxidizable component in the NADH dehydrogenase and the ubiquinone-cytochrome b site. Lipid peroxidation is a free radical-mediated degradation of polyunsaturated fatty acids. Lipid-peroxidation reactions by bovine submitochondrial particles are supported by NADH or NADPH in the presence of ADP-Fe3+ chelate. Electrons from NADH are supplied to the reactions from a component between the substrate site and the rotenone-sensitive site of the NADH dehydrogenase. The peroxidation is dependent on the rate of electron input into the respiratory chain and on the concentration of reduced ubiquinone. Alteration of inner-membrane components and damage to electron-transfer activities of submitochondrial particles are induced by lipid peroxidation. 1-Melhyl-4-phenylpyridinium (MPP+), a metabolite of a parkinsonism-inducing drug, induces NADH-dependent superoxide formation and enhances NADH-dependent lipid peroxidation in submitochondrial particles, indicating that the oxidative stress induced by MPP+ may potentiate its toxicity in dopamine neurons.

Talpade DJ, Greene JG, Higgins DS, Greenamyre JT. 2000. In vivo labeling of mitochondrial complex I (NADH : ubiquinone oxidoreductase) in rat brain using [H-3]dihydrorotenone. J Neurochem 75(6):2611-2621.
Abstract: Defects in mitochondrial energy metabolism have been implicated in several neurodegenerative disorders. Defective complex I (NADH:ubiquinone oxidoreductase) activity plays a key role in Leber's hereditary optic neuropathy and, possibly, Parkinson's disease, but there is no way to assess this enzyme in the living brain. We previously described an in vitro quantitative autoradiographic assay using [H-3]dihydrorotenone ([H-3]DHR) binding to complex I. We have now developed an in vivo autoradiographic assay for complex I using [H-3]DHR binding after intravenous administration. In vivo [H-3]DHR binding was regionally heterogeneous, and brain uptake was rapid. Binding was enriched in

neurons compared with glia, and white matter had the lowest levels of binding. In vivo [H-3]DHR binding was markedly reduced by local and systemic infusion of rotenone and was enhanced by local NADH administration. There was an excellent correlation between regional levels of in vivo [H-3]DHR binding and the in vitro activities of complex II (succinate dehydrogenase) and complex IV (cytochrome oxidase), suggesting that the stoichiometry of these components of the electron transport chain is relatively constant across brain regions. The ability to assay complex I in vivo should provide a valuable tool to investigate the status of this mitochondrial enzyme in the living brain and suggests potential imaging techniques for complex I in humans.

Tan XH, Wang SM, Xue NQ, Teng WT, Feng YQ. 2004 Jun. [Study on the risk factors and its interaction on Parkinson disease]. Zhonghua Liu Xing Bing Xue Za Zhi 25(6):527-30.
Abstract: OBJECTIVE: To explore the risk factors of Parkinson disease (PD), interaction between family history of PD and other risk factors, as well as the relative strength of genetic factors over the vulnerability of PD. METHODS: One 1:1 matched case-control study including 157 pairs of cases and controls was conducted in Qilu Hospital of Shandong University. RESULTS: Conditional logistic regression analysis showed that family history of PD, mental labor, insecticide, alcohol drinking and history of depression all had positive relationship, while smoking had a negative relationship with PD. The AP (AB)s of family history of PD and insecticide, alcohol drinking, history of depression were 55.2%, 34.0%, 41.4% and the RERIs were 8.96, 3.31, 7.85 respectively. The heritability of PD patients' first degree relatives was 36.86% +/- 5.76%, and second degree relatives was 20.66% +/- 6.81%. CONCLUSION: Family history of PD had an additive model synergism on PD, coexisting with other risk factors. Genetic factors had a smaller action on PD than environmental factors.

Tanaka T, Kohno H, Sakata K, Yamada Y, Hirose Y, Sugie S, Mori H. 2002. Modifying effects of dietary capsaicin and rotenone on 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis. Carcinogenesis 23(8):1361-1367.
Abstract: The effects of dietary administration of capsaicin and rotenone on 4-nitroquinoline 1-oxide (4-NQO)-induced tongue tumorigenesis were investigated in male F344 rats. In pilot studies, gavage with capsaicin and rotenone elevated the phase II enzymes glutathione S-transferase (GST) and quinone reductase (QR), in the liver and tongue. Also, a 10 week period of feeding of 500 p.p.m. capsaicin or rotenone together with 4-NQO exposure inhibited the occurrence of tongue dysplasia. Subsequently, a long-term study was conducted to test the protective effects of both compounds on 4-NQO-induced tongue carcinogenesis. One group was treated with 4-NQO alone (20 p.p.m. in drinking water for 8 weeks) and four other groups received the carcinogen treatment plus diets containing 500 p.p.m. test compounds for 10 weeks (initiation phase) or for 28 weeks (post-initiation phase). At the termination of the study (38 weeks), feeding of rotenone during the initiation phase, but not during the post-initiation phase, was found to significantly reduce the incidence of tongue squamous cell carcinoma (53% vs. 16%, 70% reduction, P b=e 0.0250) and severe

dysplasia (80% vs. 42%, 70% reduction, P = 0.028). Capsaicin feeding during either the initiation or promotion phase and rotenone feeding during the promotion phase also reduced the frequency of tongue carcinoma without statistical significance. The treatment with two compounds especially rotenone lowered cell proliferation activity in the tongue, elevated phase II enzymes' activities of the liver and tongue, and increased the apoptotic index of tongue carcinoma. Although our results suggest that rotenone feeding during the initiation stage prevented 4-NQO-induced tongue carcinoma, chronic intravenous exposure of rotenone reproduces several features of human Parkinson's disease in rats (Nat. Neurosci., 3, 1301-1306, 2000), suggesting that additional studies to confirm the safety of rotenone are warranted.

Tanner CM. 1992 Jul-Sep. Occupational and environmental causes of parkinsonism. Occup Med 7(3):503-13.
Abstract: Occupational causes of parkinsonism have usually been identified by direct temporal association of an exposure with disease symptoms, although recently a latent period between exposure and disease causation is being investigated. This review presents the definition of parkinsonism as contrasted with Parkinson's disease, notes the general concepts important to the consideration of toxic effects on the central nervous system, and addresses each group of agents known to cause parkinsonism, including common sources of exposure, clinical course, and proposed mechanisms of toxicity. Agents discussed include manganese, carbon disulfide, organic solvents, carbon monoxide, and MTPT and similar agents.

Tanner CM, Goldman SM. 1996. Epidemiology of Parkinson's disease. Neurol Clin 14(2):317-&.
Abstract: Parkinson's disease (PD) currently affects at least 500,000 people in the United States alone. Its prevalence is expected to triple in the next 50 years with the aging of the population. Its prevalence varies widely in community-based studies, possibly reflecting differences in risk factors among the populations studied as well as differences among study methods. Heredity, race, and gender may be risk factors. Many case-control studies show increased risk in association with rural residence, farming, and herbicide or pesticide exposure, and a decreased risk with antioxidant vitamin intake and cigarette smoking; however, the significance of these associations in regard to disease etiology is unknown.

Tawara T, Fukushima T, Hojo N, Isobe A, Shiwaku K, Setogawa T, Yamane Y. 1996. Effects of paraquat on mitochondrial electron transport system and catecholamine contents in rat brain. Arch Toxicol 70(9):585-589.
Abstract: The effects of paraquat on rat brain were studied. Activities of complex I (NADH: ubiquinone oxidoreductase) in mitochondrial electron transport system, lipid peroxidation and the amount of catecholamines in rat brain were measured after acute paraquat exposure. Complex I activities were significantly lower and lipid peroxides were higher in the brains of a paraquat-treated group than in those of a control group. Lipid peroxide in rat serum, however, did not increase after paraquat exposure.

A study of the time dependency of paraquat effects disclosed that mitochondrial complex I activities in rat brain as well as those in rat lung and liver gradually decreased prior to the appearance of respiratory dysfunction. As compared to controls, the dopamine in rat striatum was significantly lower in the paraquat-treated group. These results suggest that paraquat after crossing the blood-brain barrier might be reduced to the radical in rat brain, which may damage the brain tissue, especially dopaminergic neurons in striatum. We therefore propose that cerebral damage should be taken into consideration on paraquat exposure. Patients may therefore need to be followed up after exposure to high doses of paraquat.

Taylor CA, Saint-Hilaire MH, Cupples LA, Thomas CA, Burchard AE, Feldman RG, Myers RH. 1999. Environmental, medical, and family history risk factors for Parkinson's disease: A new England-based case control study. Am J Med Genet 88(6): 742-749.
Abstract: Controversy persists about the etiology of Parkinson's disease (PD), Pesticides, herbicides, well-water consumption, head injury, and a family history of PD have been reported as risk factors for PD. The purpose of this study was to (1) investigate the impact of environmental factors on PD risk (2) estimate the chronology, frequency, and duration of those exposures associated with PD; and (3) investigate the effects of family history on PD risk, One-hundred and forty PD cases were recruited from Boston University Medical Center. The control group was composed of 147 friends and in-laws of PD patients. Environmental, medical, and family history data were obtained by structured interview from each participant for events recalled prior to PD onset for cases, or corresponding censoring age for controls (mean age = 56 years of age for each group), A traditional stratified analysis, adjusting for birth cohort and sex, was employed, Four factors were associated with increased risk for PD: (1) head injury (OR=6.23, confidence interval [CI]: 2.58-15.07); (2) family history of PD (OR=6.08, CI: 2.35-15.58);.(3) family history of tremor (OR=3.97, CI: 1.17-13.50); and (4) history of depression (OR=3.01, CI: 1.32-6.88). A mean latency of 36.5 (SE=2.81) years passed between the age of first reported head injury and PD onset, A mean latency of 22 (SE=2.66) years passed between the onset of the first reported symptoms of depression and onset of PD, Years of education, smoking, and well-water intake were inversely associated with PD risk. PD was not associated with exposure to pesticides or herbicides, These findings support the role of both environmental and genetic factors in the etiology in PD, The results are consistent with a multifactorial model, Am. J, Med, Genet. (Neuropsychiatr, Genet,) 88:742-749, 1999, (C) 1999 Wiley-Liss, Inc.

Taylor MC, Le Couteur DG, Mellick GD, Board PG. 2000. Paraoxonase polymorphisms, pesticide exposure and Parkinson's disease in a Caucasian population. J Neural Transm 107(8-9):979-983.
Abstract: Parkinson's disease (PD) has been associated with exposure to pesticides and oxidative injury. The involvement of paraoxonase in both pesticide metabolism and lipid peroxidation suggests that it may play a role in the pathogenesis of PD. We examined the frequency of polymorphic

alleles of the PON1 and PON2 genes in a sample of caucasian subjects with PD. The frequency distribution of these genotypes did not differ significantly between patients and controls, including those who had reported exposure to pesticides.

Terzi A, Iraz M, Sahin S, Ilhan A, Idiz N, Fadillioglu E. 2004. Protective effects of erdosteine on rotenone-induced oxidant injury in liver tissue. Toxicol Ind Health 20(6-10):141-147.
Abstract: Rotenone, an insecticide of botanical origin, causes toxicity through inhibition of complex I of the respiratory chain in mitochondria. This study was undertaken to determine whether rotenone-induced liver oxidant injury is prevented by erdosteine, a mucolytic agent showing antioxidant properties. There were four groups of Male Wistar Albino rats: group one was untreated as control; the other groups were treated with erdosteine (50 mg/kg per day, orally), rotenone (2.5 mg/mL once and 1 mL/kg per day for 60 days, i.p.) or rotenone plus erdosteine, respectively. Rotenone treatment without erdosteine increased xanthine oxidase (XO) enzyme activity and also increased lipid peroxidation in liver tissue ($P < 0.05$). The rats treated with rotenone plus erdosteine produced a significant decrease in lipid peroxidation and XO activities in comparison with rotenone group ($P < 0.05$). Erdosteine treatment with rotenone led to an increase in catalase (CAT) and superoxide dismutase (SOD) activities in comparison with the rotenone group ($P < 0.05$). There was no significant difference in nitric oxide (NO) level between groups. There were negative correlations between CAT activity and malondialdehyde (MDA) level ($r = -0.934$, $P < 0.05$) with between CAT and SOD activities ($r = -0.714$, $P < 0.05$), and a positive correlation between SOD activity and MDA level ($r = 0.828$, $P < 0.05$) in rotenone group. In the rotenone plus erdosteine group, there was a negative correlation between XO activity and NO level in liver tissue ($r = -0.833$, $P < 0.05$). In the light of these findings, erdosteine may be a protective agent for rotenone-induced liver oxidative injury in rats.

Testa CM, Sherer TB, Greenamyre JT. 2005. Rotenone induces oxidative stress and dopaminergic neuron damage in organotypic substantia nigra cultures. Molecular Brain Research 134(1):109-118.
Abstract: Rotenone, a pesticide and complex I inhibitor, causes nigrostriatal degeneration similar to Parkinson disease pathology in a chronic, systemic, in vivo rodent model [M. Alam, W.J. Schmidt, Rotenone destroys dopaminergic neurons and induces parkinsonian symptoms in rats, Behav. Brain Res. 136 (2002) 317-324; R. Betarbet, T.B. Sherer, G. MacKenzie, M. Garcia-Osuna, A.V PaDov, J.T. Greenamyre, Chronic systemic pesticide exposure reproduces features of Parkinson's disease, Nat. Neurosci. 3 (2000) 1301-1306; S.M. Fleming, C. Zhu, P.O. Fernagut, A. Mchta, C.D. DiCarlo, R.L. Seaman, M.F. Chesselet, Behavioral and immunohistochemical effects of chronic intravenous and subcutaneous infusions of varying doses of rotenone, Exp. Neurol. 187 (2004) 418-429; T.B. Sherer, J.H. Kim, R. Betarbet, J.T. Greenamyre, Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation, Exp. Neural. 179 (2003) 9-16.]. To better investigate the role of mitochondria and complex I inhibition in chronic,

progressive neurodegenerative disease, we developed methods for long-term culture of rodent postnatal midbrain organotypic slices. Chronic complex I inhibition over weeks by low dose (10-50 nM) rotenone in this system lead to dose- and time-dependent destruction of substantia nigra pars compacta neuron processes, morphologic changes, some neuronal loss, and decreased tyrosine hydroxylase (TH) protein levels. Chronic complex I inhibition also caused oxidative damage to proteins, measured by protein carbonyl levels. This oxidative damage was blocked by the antioxidant alpha-tocopherol (vitamin E). At the same time, alpha-tocopherol also blocked rotenone-induced reductions in TH protein and TH immunohistochemical changes. Thus, oxidative damage is a primary mechanism of mitochondrial toxicity in intact dopaminergic neurons. The organotypic culture system allows close study of this and other interacting mechanisms over a prolonged time period in mature dopaminergic neurons with intact processes, surrounding glia, and synaptic connections. (C) 2004 Elsevier B.V. All rights reserved.

Thakar JH, Hassan MN. 1988. Effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), cyperquat (MPP+) and paraquat on isolated mitochondria from rat striatum, cortex and liver. Life Sci 43(2):143-9.
Abstract: The effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), its metabolite 1-methyl-4-phenyl pyridinium ion (MPP+, cyperquat) and a structurally-related compound paraquat on mitochondrial functions were investigated in isolated organelles from rat striatum, cortex and liver. MPTP (0.1-1.0 mM) had no significant effect on various parameters of mitochondrial oxidative phosphorylation. In contrast, MPP+ (0.5 mM) inhibited the oxidation of the nicotinamide adenine dinucleotide (NAD+)-linked substrates pyruvate and malate but not that of the flavin adenine dinucleotide (FAD+)-linked substrate succinate. Paraquat (5.0 mM) significantly stimulated basal oxygen consumption (state 4) without influencing the oxygen utilization (state 3) associated with adenosine diphosphate (ADP) phosphorylation. Thus, these structurally-related compounds have different effects on mitochondrial oxidative phosphorylation, but the organelles from striatum, cortex and liver were affected in a similar manner by these compounds.

Thiffault C, Langston JW, Di Monte DA. 2000. Increased striatal dopamine turnover following acute administration of rotenone to mice. Brain Res 885 (2):283-288.
Abstract: Because of the potential role of mitochondrial dysfunction in nigrostriatal degeneration in Parkinson's disease, the effects of rotenone tan inhibitor of mitochondrial NADH dehydrogenase and a naturally occurring toxicant) on the levels of striatal dopamine (DA) and DA metabolites were evaluated after acute and subchronic administration to mice. Systemic acute treatment with relatively high doses of rotenone did not affect DA concentration, but caused a significant increase in both DA metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). DOPAC and HVA changes were measured at 1 day and were reversed within 1 week. paralleling the time course of rotenone-induced increase in striatal lactate levels. Subchronic administration with a

relatively mild dose of rotenone did not significantly alter the striatal levels of DA and DOPAC, while it slightly reduced HVA concentration. No neurochemical signs of dopaminergic damage were seen when mice were co-exposed to rotenone and diethyldithiocarbamate, a compound known to enhance nigrostriatal injury caused by the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Also, rotenone did not cause additional injury to animals previously lesioned by MPTP. Taken together, data indicate that rotenone is not capable of causing overt dopaminergic toxicity under the testing paradigms used in this study. Rather, an increase in DA turnover, as indicated by a higher (DOPAC+HVA)/DA ratio, seems to be associated to rotenone-induced striatal energy impairment. (C) 2000 Elsevier Science B.V. All rights reserved.

Thiffault C, Langston WJ, Di Monte DA. 2001 Nov. Acute exposure to organochlorine pesticides does not affect striatal dopamine in mice. Neurotox Res 3(6):537-43.
Abstract: The purpose of this study was to evaluate the possible association between the risk of developing Parkinson's disease (PD) and exposure to organochlorine pesticides in the mouse model. Animals were treated with a single subcutaneous injection of either dieldrin (40 and 80 mg/kg) or 2,4-dichlorophenoxyacetic acid (100 and 200 mg/kg, 2,4-D) and levels of dopamine (DA) and DA metabolites were measured in the striatum at the 7-day time point. Dieldrin exposure did not affect the striatal concentrations of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Administration of 2,4-D did not produce any changes with the exception of a slight (15%), but statistically significant decrease in DOPAC using the higher dose of the pesticide. No neurochemical signs of dopaminergic injury were found following the combined treatment with either dieldrin or 2,4-D plus diethyldithiocarbamate (DDC), a compound known to potentiate the effects of the dopaminergic toxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Furthermore, neither dieldrin nor 2,4-D caused additional damage in animals previously lesioned with MPTP. Data failed to support the hypothesis that acute exposure to organochlorine compounds or synergistic interactions involving these pesticides may cause significant damage to dopaminergic terminals and therefore contribute to nigrostriatal degeneration in PD.

Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB, Cory-Slechta DA. 2000. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? Brain Res 873(2):225-234.
Abstract: The absence of any compelling basis for a heritable basis of idiopathic Parkinson's disease (PD) has focused attention on environmental exposures as causative agents. While the herbicide paraquat has repeatedly been implicated, its impact on dopamine systems following systemic exposures is equivocal. The restricted focus on paraquat also ignores the extensive geographical overlap of its use with other agrichemicals known to adversely impact dopamine systems, including ethylenebisdithiocarbamate fungicides such as maneb. The present study

sought to determine whether combined exposures to paraquat and maneb would produce additive effects and support a multiple-hit environmental contribution to PD. C57BL/6 mice were exposed to either paraquat (5-10 mg/kg) or maneb (15-30 mg/kg) i.p. alone or in combination once a week for 4 weeks. Sustained decreases in motor activity immediately following injections were consistently observed only with combined exposures, with activity levels returning to control values 24 h later. Concurrently, levels of dopamine and metabolites and dopamine turnover were increased immediately post-injection only by combined exposures, and returned to control levels or below within 48 h. Reductions in tyrosine hydroxylase immunoreactivity, measured 3 days after the last injection, resulted only from combined exposure and were detected in dorsal striatum, but not in the nucleus accumbens. The fact that combined exposures resulted in potentiated effects that appear to target nigrostriatal dopamine systems suggests that these combinations may be important environmental risk factors for Parkinsonism. These findings also raise questions about the adequacy of current risk assessment guidelines for these chemicals which are based on effect levels derived from exposures to single agents. 

Thiruchelvam M, Mccormack A, Richfield EK, Baggs RB, Tank AW, Di Monte DA, Cory-Slechta DA. 2003. Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. Eur J Neurosci 18(3):589-600.
Abstract: While advancing age is the only unequivocally accepted risk factor for idiopathic Parkinson's disease, it has been postulated that exposure to environmental neurotoxicants combined with ageing could increase the risk for developing Parkinson's disease. The current study tested this hypothesis by exposing C57BL/6 mice that were 6 weeks, 5 months or 18 months old to the herbicide paraquat, the fungicide maneb or paraquat + maneb, a combination that produces a Parkinson's disease phenotype in young adult mice. Paraquat + maneb-induced reductions in locomotor activity and motor coordination were age dependent, with 18-month-old mice most affected and exhibiting failure to recover 24 h post-treatment. Three months post-treatment, reductions in locomotor activity and deficits in motor coordination were sustained in 5-month-old and further reduced in 18-month-old paraquat + maneb groups. Progressive reductions in dopamine metabolites and dopamine turnover were greatest in 18-month-old paraquat + maneb and paraquat groups 3 months post-treatment. Increased tyrosine hydroxylase enzyme activity compensated for striatal tyrosine hydroxylase protein and/or dopamine loss following treatment in 6-week-old and 5-month-old, but not 18-month-old paraquat and paraquat + maneb mice. Numbers of nigrostriatal dopaminergic neurons were reduced in all age groups following paraquat alone and paraquat + maneb exposure, but these losses, along with decreases in striatal tyrosine hydroxylase protein levels, were progressive in 18-month-old paraquat and paraquat + maneb groups between 2 weeks and 3 months post-exposure. Collectively, these data demonstrate enhanced sensitivity of the ageing nigrostriatal dopamine pathway to these

pesticides, particularly paraquat + maneb, resulting in irreversible and progressive neurotoxicity.

Thiruchelvam M, Prokopenko O, Cory-Slechta DA, Richfield EK, Buckley B, Mirochnitchenko O. 2005. Overexpression of superoxide dismutase or glutathione peroxidase protects against the paraquat plus maneb-induced Parkinson disease phenotype. J Biol Chem 280(23):22530-22539.
Abstract: Oxidative stress has been implicated in the pathogenesis of Parkinson disease based on its role in the cascade of biochemical changes that lead to dopaminergic neuronal death. This study analyzed the role of oxidative stress as a mechanism of the dopaminergic neurotoxicity produced by the combined paraquat and maneb model of the Parkinson disease phenotype. Transgenic mice overexpressing either Cu, Zn superoxide dismutase or intracellular glutathione peroxidase and non-transgenic mice were exposed to saline, paraquat, or the combination of paraquat + maneb twice a week for 9 weeks. Non-transgenic mice chronically exposed to paraquat + maneb exhibited significant reductions in locomotor activity, levels of striatal dopamine and metabolites, and dopaminergic neurons in the substantia nigra pars compacta. In contrast, no corresponding effects were observed in either Cu, Zn superoxide dismutase or glutathione peroxidase transgenic mice. Similarly, the increase in levels of lipid hydroperoxides in the midbrain and striatum of paraquat + maneb- treated non-transgenic mice was not detected in either Cu, Zn superoxide dismutase or glutathione peroxidase transgenic mice. To begin to determine critical pathways of paraquat + maneb neurotoxicity, the functions of cell death- inducing and protective mechanisms were analyzed. Even a single injection of paraquat + maneb in the non-transgenic treated group modulated several key pro- and antiapoptotic proteins, including Bax, Bad, Bcl-xL, and upstream stress-induced cascade. Collectively, these findings support the assertion that protective mechanisms against paraquat + maneb- induced neurodegeneration could involve modulation of the level of reactive oxygen species and alterations of the functions of specific signaling cascades.

Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. 2000. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: Implications for Parkinson's disease. J Neurosci 20(24):9207-9214.
Abstract: Experimental evidence supporting 1,1'-dimethyl-4,4'-bipyridinium [paraquat (PQ)] as a risk factor for Parkinson's disease (PD) is equivocal. Other agricultural chemicals, including dithiocarbamate fungicides such as manganese ethylenebisdithiocarbamate [maneb (MB)], are widely used in the same geographical regions as paraquat and also impact dopamine systems, suggesting that mixtures may be more relevant etiological models. This study therefore proposed that combined PQ and MB exposures would produce greater effects on dopamine (DA) systems than would either compound administered alone. Male C57BL/6 mice were treated twice a week for 6 weeks with intraperitoneal saline, 10 mg/kg paraquat, 30 mg/kg maneb, or their combination (PQ 1 MB). MB, but not

PQ, reduced motor activity immediately after treatment, and this effect was potentiated by combined PQ 1 MB treatment. As treatments progressed, only the combined PQ 1 MB group evidenced a failure of motor activity levels to recover within 24 hr. Striatal DA and dihydroxyphenylacetic acid increased 1-3 d and decreased 7 d after injections. Only PQ 1 MB reduced tyrosine hydroxylase (TH) and DA transporter immunoreactivity and did so in dorsal striatum but not nucleus accumbens. Correspondingly, striatal TH protein levels were decreased only by combined PQ 1 MB 5 d after injection. Reactive gliosis occurred only in response to combined PQ 1 MB in dorsal-medial but not ventral striatum. TH immunoreactivity and cell counts were reduced only by PQ 1 MB and in the substantia nigra but not ventral tegmental area. These synergistic effects of combined PQ 1 MB, preferentially expressed in the nigrostriatal DA system, suggest that such mixtures could play a role in the etiology of PD.

Thiruchelvam M, Richfield EK, Goodman BM, Baggs RB, Cory-Slechta DA. 2002. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology 23(4-5):621-633. Abstract: Idiopathic Parkinson's disease (PD) is associated with advanced age, but it is still unclear whether dopaminergic neuronal death results from events initiated during development, adulthood, or represents a cumulative effect across the span of life. This study hypothesized that paraquat (PQ) and maneb (MB) exposure during critical periods of development could permanently change the nigrostriatal dopamine (DA) system and enhance its vulnerability to subsequent neurotoxicant challenges. C57BL/6 mice were treated daily with saline, 0.3 mg/kg PQ, I mg/kg MB or PQ + MB from post-natal (PN) days 5 to 19. At 6 weeks, a 20% decrease in activity was evident only in the PQ + MB group, with a further decline (40%) observed at 6 months. A subset of mice were re-challenged as adults with saline, 10 mg/kg PQ, 30 mg/kg MB, or PQ + MB 2 x a week for 3 weeks. Mice exposed developmentally to PQ + MB and re-challenged as adults were the most affected, showing a 70% reduction in motor activity 2 weeks following the last re-challenge dose. Striatal DA levels were reduced by 37% following developmental exposure to PQ + MB only, but following adult re-challenge levels were reduced by 62%. A similar pattern of nigral dopaminergic cell loss was observed, with the PQ + MB treated group exhibiting the greatest reduction, with this loss being amplified by adult re-challenge. Developmental exposure to PQ or MB alone produced minimal changes. However following adult re-challenge, significant decreases in DA and nigral cell counts were observed, suggesting that exposure to either neurotoxicant alone produced a state of silent toxicity that was unmasked following adult re-exposure. Taken together these findings indicate that exposure to pesticides during the PN period can produce permanent and progressive lesions of the nigrostriatal DA system, and enhanced adult susceptibility to these pesticides, suggesting that developmental exposure to neurotoxicants may be involved in the induction of neurodegenerative disorders and/or alter the normal aging process. 

Thiruchelvam MJ, Barlow BK, Richfield EK, Cory-Slechta DA. 2003. Developmental pesticide exposures and subsequent vulnerability to the Parkinson's disease phenotype. Neurotoxicology 24(2):292.

Thiruchelvam MJ, Powers JM, Cory-Slechta DA, Richfield EK. 2004. Risk factors for dopaminergic neuron loss in human alpha-synuclein transgenic mice. Eur J Neurosci 19(4):845-854.
Abstract: Genetic background, pesticide exposure, age, gender, diet and lifestyle are implicated risk factors in Parkinson's disease. We demonstrate dopamine neuron loss and other features of Parkinsonism based on the interaction of several of these human risk factors in transgenic mice expressing human alpha-synuclein. Mice expressing different forms of human alpha-synuclein had progressive declines in locomotor activity and abnormal responses to apomorphine that were modified by transgenic status. Stereological counts of tyrosine hydroxylase-positive neurons significantly declined with age only in the transgenic lines, consistent with a constant or decreasing risk, with the line expressing a double-mutant form of human alpha-synuclein more severely affected than the line expressing wild-type human alpha-synuclein. Treatment with Mn2+-ethylenebisdithiocarbamate and paraquat resulted in significantly greater effects in the double-mutant line than the other lines. Inclusions were not identified in the transgenic lines. Overexpression of human alpha-synuclein had adverse effects on substantia nigra pars compacta dopaminergic neurons that were modified by risk factors interacting in humans, including human alpha-synuclein mutations, ageing, and exposure to pesticides.

Tiesong SS, Joseph J, Hillard CJ, Kalyanaraman B. 2005. Death-associated protein kinase as a sensor of mitochondrial membrane potential - Role of lysosome in mitochondrial toxin-induced cell death. J Biol Chem 280(41): 34644-34653.
Abstract: We have investigated here the mechanism of dephosphorylation and activation of death-associated protein kinase ( DAPK) and the role of lysosome in neuroblastoma cells (SH-SY5Y) treated with mitochondrial toxins, such as MPP+ and rotenone. Mitochondrial respiratory chain inhibitors and uncouplers decreased mitochondrial membrane potential leading to DAPK dephosphorylation and activation. The class III phosphoinositide 3-kinase inhibitors attenuated DAPK dephosphorylation induced by mitochondrial toxins. Complex I inhibition by mitochondrial toxins ( e. g. MPP+) resulted in mitochondrial swelling and lysosome reduction. Inhibition of class III phosphoinositide 3-kinase attenuated MPP +-induced lysosome reduction and cell death. The role of DAPK as a sensor of mitochondrial membrane potential in mitochondrial diseases was addressed.

Tomas-Camardiel M, Herrera AJ, Venero JL, Sanchez-Hidalgo MC, Cano J, Machado A. 2002. Differential regulation of glutamic acid decarboxylase mRNA and tyrosine hydroxylase mRNA expression in the aged manganese-treated rats. Molecular Brain Research 103(1-2):116-129.
Abstract: Recent studies have implicated chronic elevated exposures to environmental agents, such as metals (e.g. manganese, Mn) and

pesticides, as contributors to neurological disease. Eighteen-month-old rats received intraperitoneal injections of manganese chloride (6 mg Mn/kg/day) or equal volume of saline for 30 days in order to study the effect of manganese on the dopamine- and GABA-neurons. The structures studied were substantia nigra, striatum, ventral tegmental area, nucleus accumbens and globus pallidus. First, we studied the enzymatic activity of mitochondrial complex 11 succinate dehydrogenase (SDH). We found an overall decrease of SDH in the different brain areas analyzed. We then studied the mRNA levels for tyrosine hydroxylase (TH) and the dopamine transporter (DAT) by in situ hybridization. TH mRNA but not DAT mRNA was significantly induced in substantia nigra and ventral tegmental area following Mn treatment. Correspondingly, TH immunoreactivity was increased in substantia nigra and ventral tegmental area. Manganese treatment significantly decreased GAD mRNA levels in individual GABAergic neurons in globus pallidus but not in striatum. We also quantified the density of glial fibrillary acidic protein (GFAP)-labeled astrocytes and OX-42 positive cells. Reactive gliosis in response to Mn treatment occurred only in striatum and substantia nigra and the morphology of the astrocytes was different than in control animals. These results suggest that the nigrostriatal system could be specifically damaged by manganese toxicity. Thus, changes produced by manganese treatment on 18-month-old rats could play a role in the etiology of Parkinson's disease. (C) 2002 Elsevier Science B.V. All rights reserved.

Trojanowski JQ. 2003. Commentary - Rotenone neurotoxicity: A new window on environmental causes of Parkinson's disease and related brain amyloidoses. Exp Neurol 179(1):6-8.

Tsai CH, Lo SK, See LC, Chen HZ, Chen RS, Weng YH, Chang FC, Lu CS. 2002. Environmental risk factors of young onset Parkinson's disease: a case-control study. Clin Neurol Neurosurg 104(4):328-333.
Abstract: While the cause of Parkinson's disease (PD) remains unknown, recent evidence suggests certain environmental factors, such as well water drinking, herbicides and pesticides exposure, and neurotoxins, may trigger the chain of oxidative reactions culminating in the death of dopaminergic neurons in substantia nigra to cause parkinsonism. Most studies to date focused on PD with old age onset. However, there is a peculiar group of parkinsonian patients, the young onset Parkinson's disease (YOPD), in whom the age of onset is before 40. It is intriguing to know whether earlier exposure to the putative neurotoxin(s) may contribute to the earlier onset. We therefore conducted this case-control study in which 60 PD patients, 30 YOPD patients and the same number of age- and sex-matched young controls were included. Using logistic regression, we found well water drinking and head injury were risk factors for the development of YOPD. When YOPD patients were compared with PD, we found head injury and exercise were the significant predictors. Keeping all other variables constant, head injury was a risk factor and exercise appeared to be a protective factor. We conclude early exposure to well water drinking and head trauma may trigger and expedite the appearance of parkinsonian features, but such acceleration may be prevented through regular

exercise. (C) 2002 Elsevier Science B.V. All rights reserved.

Tsai MJ, Lee EHY. 1998. Nitric oxide donors protect cultured rat astrocytes from 1-methyl-4-phenylpyridinium-induced toxicity. Free Radic Biol Med 24(5): 705-713.
Abstract: MPP+ is thought to mediate MPTP's toxicity on dopamine neurons by inhibiting mitochondrial respiration. However, astrocytic injuries are also observed in MPTP/MPP+-treated rats. Because nitric oxide (NO.) is suggested to be cytoprotective, we examined the effects of nitroprusside (SNP), S-nitroso-N-acetylpenicillamine (SNAP), and 3-morpholinosydnonimine (SIN-1) on MPP+ induced toxicity in astrocytes. Incubation of astrocytes with MPP+ for 2 days produced a dose-dependent toxicity, including increase in lactate level and lipid peroxidation, decrease of metabolic activity and cell damage. SNP, SNAP, and SIN-1 all attenuated MPP+-induced toxicity. The same protection was not achieved with N-acetylpenicillamine or ferrocyanide, structural analogues of SNAP or SNP but devoid of NO.. Further, the effect was not attributed to the increased cGMP levels or blockade of MPP+ accumulation in astrocytes. Notably, catalase, dimethyl sulfoxide and ferricyanide, an extracellular electron acceptor, were also effective in inhibiting MPP+ damage. NO. donors and analogues were also tested against damage produced by rotenone, an irreversible complex I inhibitor. Only ferricyanide and SNP effectively protected rotenone's toxicity. These results concluded that (1) NO. may protect astrocytes from MPP+-induced free radical formation, and (2) prevention of energy depletion/free radicals production alleviate MPP+-induced toxicity. (C) 1998 Elsevier Science Inc.

Tsuda T, Sugaya A, Liu YZ, Katoh K, Tanaka K, Kawazura H, Sugaya E, Kusai M, Kohno M. 1994. Radical scavenger effect of boschniakia-rossica. J Ethnopharmacol 41(1-2):85-90.
Abstract: To elucidate the mechanism of the invigorating and antisenile action of the dried herb of Boschniakia rossica (Boschniakiae Herba), the free radical scavenging activity of its 50% ethanol extract (BR) was examined using an electron spin resonance spectrometer. The scavenging activity of plasma from Fisher-334 rats with continuous administration of BR was also examined. The concentrations showing 50% inhibition of the free radical of BR on the 1,1 -diphenyl-2-picrylhydrazil (DPPH) radical, superoxide radical and hydroxyl radical were 0.003%, 0.06% and 9.67%, respectively. Plasma from the rats with BR administered clearly showed higher free radical scavenging activity compared with that of normal control rats. These findings suggest that Boschniakia rossica has strong free radical scavenging activity and consequently it has inhibitory effects on the disorders caused by free radical production in living tissue.

Tvedt B, Krogstad JM, Berstad J. 1996 Oct 20. [Hypoxic brain damage after carbon monoxide poisoning. Visual agnosia, reduced initiative and memory and delayed sequelae]. Tidsskr Nor Laegeforen 116(25):3005-8.
Abstract: Four patients with hypoxic brain damage caused by carbon monoxide poisoning are described. Three of these had attempted suicide with car exhaust fumes. Two patients had visual agnosia due to lesions in

the parieto-occipital cortex. Three patients had temporary Parkinsonian symptoms. In two of these patients CT and MRI showed lesions in the globus pallidus. They also showed reduced initiative, and in one patient this was combined with minor tics and obsessive symptoms. One patient had impaired memory as the only symptom. The patient with the longest lasting exposure developed delayed sequelae; three weeks after the poisoning he became apathetic and confused, with failing memory, Parkinsonian symptoms, and urinary and faecal incontinence. MRI showed demyelination in the periventricular white matter. His condition started to improve two months after the accident.

Twombly R. 2004. Pesticides and Parkinson disease. Environ Health Perspect 112 (10):A548.

Uitti RJ, Rajput AH, Ashenhurst EM, Rozdilsky B. 1985 Jun. Cyanide-induced parkinsonism: a clinicopathologic report. Neurology 35(6):921-5.
Abstract: An 18-year-old man ingested 975 to 1,300 mg of potassium cyanide in a suicide attempt. He was treated and survived the poisoning episode, but then had severe parkinsonian syndrome, characterized primarily by akinesia and rigidity. He died 19 months after the drug overdose. At autopsy, major destructive changes were found in the globus pallidus and putamen, whereas the melanin-containing zone of substantia nigra was intact. This is the first clinicopathologic report of parkinsonism as a result of cyanide poisoning.

Uversky VN. 2004. Neurotoxicant-induced animal models of Parkinson's disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration. Cell Tissue Res 318(1):225-241.
Abstract: The etiologic basis of Parkinson's disease (PD), the second most common age-related neurodegenerative disorder, is unknown. Recent epidemiological and experimental studies indicate that exposure to environmental agents, including a number of agricultural chemicals, may contribute to the pathogenesis of this disorder. Animal models are important tools in experimental medical science for studying the pathogenesis and therapeutic intervention strategies of human diseases. Since many human disorders do not arise spontaneously in animals, characteristic functional changes have to be mimicked by neurotoxic agents. Recently, agricultural chemicals, when administrated systemically, have been shown to reproduce specific features of PD in rodents, thus opening new routes for the development of animal models for this disorder. In addition to a brief historical overview of the toxin-induced PD models, this study provides a detailed description of exiting models in which Parkinsonism is initiated via the exposure of animals to such agricultural chemicals as rotenone, paraquat, and maneb. Suggested neurotoxicity mechanisms of these chemicals are considered, and the major lessons learned from the analysis of pesticide-induced PD models are discussed.

Uversky VN, Li J, Bower K, Fink AL. 2002. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: Implications for Parkinson's

disease. Neurotoxicology 23(4-5):527-536.
Abstract: Aggregation of alpha-synuclein has been implicated in the formation of proteinaceous inclusions in the brain (Lewy bodies, Lewy neurites) that are characteristic of neurodegenerative diseases, such as Parkinson's disease (PD) and dementia with Lewy bodies (DLBs). The etiology of PD is unknown, but recent work has shown that except in rare cases, there appears to be no direct genetic basis. However, several studies have implicated environmental factors, especially pesticides and metals. Here we show that certain pesticides and metals induce a conformational change in a-synuclein and directly accelerate the rate of formation of alpha-synuclein fibrils in vitro. In addition, the simultaneous presence of metal and pesticide led to synergistic effects on the rate of fibrillation. We propose a model in which environmental factors in conjunction with genetic susceptibility may form the underlying molecular basis for idiopathic PD. (C) 2002 Elsevier Science Inc. All rights reserved.

Uversky VN, Li J, Fink AL. 2001. Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease. FEBS Lett 500(3):105-108.
Abstract: Parkinson's disease involves intracellular deposits of alpha -synuclein in the form of Lewy bodies and Lewy neurites, The etiology of the disease is unknown, however, several epidemiological studies have implicated environmental factors, especially pesticides. Here we show that several pesticides, including rotenone, dieldrin and paraquat, induce a conformational change in alpha -synuclein and significantly accelerate the rate of formation of alpha -synuclein fibrils in vitro, We propose that the relatively hydrophobic pesticides preferentially bind to a partially folded intermediate conformation of alpha -synuclein, accounting for the observed conformational changes, and leading to association and subsequent fibrillation, These observations suggest one possible underlying molecular basis for Parkinson's disease. (C) 2001 Published by Elsevier Science B.V. on behalf of the Federation of European Biochemical Societies.

Vaccari A, Saba PL. 1995. The tyramine-labeled vesicular transporter for dopamine - a putative target of pesticides and neurotoxins. European Journal of Pharmacology-Environmental Toxicology and Pharmacology Section 292(3-4):309-314.
Abstract: This study defined the ability of a large sample of heterogeneous pesticides and neurotoxins to interact with the [H-3]tyramine-labelled vesicular transporter of dopamine in rat striatum. Botanical (with rotenone as the most potent), and organochlorine (Kepone) insecticides, as well as fungicides (Zineb), as a whole, consistently inhibited [H-3]tyramine binding, with K-i values ranging from 5 nM to 10 mu M. ATP/Mg2+-dependent [H-3]tyramine uptake to purified striatal synaptic vesicles was also inhibited by rotenone. Organophosphate and carbamate insecticides, and miscellaneous herbicides poorly antagonized [H-3]tyramine binding, yielding K-i values exceeding 10 mu M. Several, though not all, of the best recognized central neurotoxins tested were major binding antagonists. Their rank order of potency was 1-methyl-4-phenylpyridinium ion (MPP(+)) > trimethyltin greater than or equal to 6-hydroxydopamine > N-(2-

chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) > 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), with K-i values ranging from 35 nM to 3 mu M. Overall, the potent interaction of selected pesticides and chemicals with the vesicular transporter for dopamine, although, by itself, not synonymous with neurotoxicity, would argue for a likely impairment of transmitter homeostasis, or the putative formation of neurodegenerative toxin pools.

Vaglini F, Fascetti F, Fornai F, Maggio R, Corsini GU. 1994. (+)Mk-801 prevents the ddc-induced enhancement of mptp toxicity in mice. Brain Res 668(1-2): 194-203.
Abstract: In order to reach deeper insight into the mechanism of diethyldithiocarbamate (DDC)-induced enhancement of MPTP toxicity in mice, MK-801, a non-competitive antagonist of NMDA receptors, has been used as a tool to study the role of excitatory amino acids. In agreement with previous reports, (+)MK-801 did not significantly affect either striatal dopamine (DA) or tyrosine-hydroxylase (TH) activity in MPTP-treated animals. On the contrary (+)MK-801, but not (-)MK-801 significantly reduced the DDC + MPTP-induced fail in striatal DA and TH activity. A similar preventing effect on DA metabolites (DOPAC and HVA) and HVA/DA ratio was observed. The number of TH+ neurons in the substantia nigra (SN) of(+)MK-801-pre-treated mice was not significantly different from that of control animals, indicating that this treatment specifically antagonized the extensive DDC-induced lesion of dopaminergic cell bodies in this brain area. (+)MK-801 treatment did not affect the DDC-induced changes of striatal MPP(+) levels, suggesting that the observed antagonism of MK-801 against DDC is not due to MPP(+) kinetic modifications. Pretreatment with the MAO-B inhibitor, L-deprenyl, or with the DA uptake blocker, GBR 12909, completely prevented the marked DA depletion elicited by DDC + MPTP within the striatum. Both treatments also protected from the fall in DA metabolites and TH activity as well. This indicates that DDC-induced potentiation is dependent upon MPP(+) production and its uptake by the dopaminergic nerve terminals. All these findings suggest that NMDA receptors play a crucial role in the DDC-induced enhancement of MPTP toxicity.

Vaglini F, Pardini C, Bonuccelli U, Maggio R, Corsini GU. 2003. Dextromethorphan prevents the diethyldithiocarbamate enhancement of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in mice. Brain Res 973(2): 298-302.
Abstract: In this report we show that dextromethorphan, a non-opioid cough suppressant, prevents the neurodegeneration of dopaminergic neurons in the substantia nigra of mice treated with diethyldithiocarbamate (DDC) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This effect is further substantiated by the assessment of dopamine (DA) content in the striatum of these animals. Dextromethorphan does not attenuate the striatal DA fall induced by MPTP alone but completely prevents DDC-induced enhancement after the combined treatment. Moreover, a study of DA metabolites has confirmed this neuroprotective property. The striatal levels of serotonin, which were studied as a control neuronal marker, did

not change with any of the treatments administered. Furthermore, we show that dextromethorphan reduces the toxicity of glutamate against dopamine neurons in mesencephalic cell cultures. In line with previous data suggesting that dextromethorphan can prevent neuronal damage, our observations supply new evidence regarding the possibility of this compound being of therapeutic use in neurodegenerative diseases. (C) 2003 Elsevier Science B.V. All rights reserved.

Vaglini F, Pardini C, Viaggi C, Bartoli C, Dinucci D, Corsini GU. 2004. Involvement of cytochrome P450 2E1 in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson's disease. J Neurochem 91(2):285-298.
Abstract: Elucidation of the biochemical steps leading to the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced degeneration of the nigrostriatal dopamine (DA) pathway has provided new clues to the pathophysiology of Parkinson's disease. In line with the enhancement of MPTP toxicity by diethyldithiocarbamate (DDC), here we demonstrate how other cytochrome P450 (CYP) 2E1 inhibitors, such as diallyl sulphide (DAS) and phenylethylisothiocyanate (PIC), also potentiate the selective DA neurone degeneration in C57/bl mice. In addition, we show that CYP 2E1 is present in the brain and in the basal ganglia of this mouse strain, as measured by RT-PCR, western blot analysis and immunohistochemistry. A kinetic analysis of MPTP and its metabolites, by means of the microdialysis technique in the striatum, indicates that no detoxification metabolic pathway is affected by any of these inhibitors. This does not rule out, however, that an undetected detoxification pathway involving CYP 2E1 is operating. In order to provide direct evidence for this isozyme involvement, CYP 2E1 knockout mice were challenged with MPTP or the combined treatment. Here we show that these transgenic mice have a low sensitivity to MPTP alone, similar to their wild-type counterparts, suggesting that it is likely that transgenic mice compensate for the missing enzyme. However, DDC pretreatment completely fails to enhance MPTP toxicity in CYP 2E1 knockout mice, whereas this enhancement is regularly present in wild-type animals. This study indicates that the occurrence of CYP 2E1 in C57/bl mouse brain is relevant to MPTP toxicity, and suggests that this isozyme may have a detoxificant role related to the efflux transporter of the toxin.

Vanacore N. 2005. Epidemiological evidence on multiple system atrophy. J Neural Transm 112(12):1605-1612.
Abstract: Multiple system atrophy (MSA), is a sporadic neurodegenerative disorder characterized clinically by any combination of parkinsonian, autonomic, cerebellar or pyramidal symptoms and signs. The frequence of disease is estimated for the incidence rate to 0.6 cases per 100.000 person-years, while the prevalence rate is included between 1.86 and 4.9 cases per 100.000 pop. A risk factor seems to be the occupational history of farming also if the occupational exposure to pesticides is not associated with MSA. Smoking is probably a protective factor in MSA as Parkinson's disease. MSA seems a sporadic disease also if recently a German family with two MSA cases has been reported. The polymorphism association

studies support a role for inflammation-related genes in risk for MSA. The current epidemiological and clinical evidence suggests that likely the etiopathogenesis of MSA is complex, and that many genetic as well as environmental factors are involved. Unfortunately, the most of studies in MSA are lacking in a sample size estimate to test the hypothesis, then the scientific evidence is poor. Then, much larger numbers of cases and controls are necessary for these studies to reach sufficient power, but collecting such large numbers is feasible only in the framework of multicentric consortia.

Vanacore N, Bonifati V, Fabbrini G, Colosimo C, De Michele G, Marconi R, Nicholl D, Locuratolo N, Talarico G, Romano S, Stocchi F, Bonuccelli U, De Mari M, Vieregge P, Meco G. 2001. Epidemiology of multiple system atrophy. ESGAP Consortium. European Study Group on Atypical Parkinsonisms. Neurological Sciences 22(1):97-99.
Abstract: Multiple system atrophy (MSA) is a form of atypical parkinsonism with unknown etiology. The epidemiological studies conducted up to now on this disease are scarce. The incidence rate is about 0.6 cases per 100 000 persons per year. The prevalence rates show 4-5 cases per 100 000 persons. In Italy, about 4900 prevalent cases have been estimated. The mean onset age is about 54 years; the median survival is 7-9 years. Only one case-control study has been performed on this disease. This study showed an increased risk of MSA associated with occupational exposure to organic solvents, plastic monomers and additives, pesticides and metals. Smoking habits seem to be less frequent in MSA cases (as in Parkinson's disease cases) than in healthy controls. Quinn's clinical criteria and those of the Consensus Conference promoted by the American Academy of Neurology are in fair agreement. We have performed a case-control study on 73 MSA cases, 146 hospital controls and 73 population controls.

Vanacore N, Nappo A, Gentile M, Brustolin A, Palange S, Liberati A, Di Rezze S, Caldora G, Gasparini M, Benedetti F, Bonifati V, Forastiere F, Quercia A, Meco G. 2002 . Evaluation of risk of Parkinson's disease in a cohort of licensed pesticide users. Neurological Sciences 23:S119-S120.
Abstract: In the last two years, the environmental theory on the aetiology of Parkinson disease has acquired new data. From an experimental point of view, a new model of parkinsonism induced by rotenone, a diffuse. insecticide, has been proposed, and in vitro studies have provided proof that several pesticides stimulate the formation of a-synuclein fibrils (one of the principal constituents of Lewy bodies). Moreover, a meta-analysis of all case-control studies so far performed showed a positive, statistically significant association between pesticide exposure and PD. In this context, we are performing a cohort study on 5575 licensed pesticide users in the province of Viterbo. After 27 years of follow-up, 4788 subjects are still alive. The aim of this study is to measure the prevalence of Parkinson's disease in a large group of workers with theoretically increased risk.

Ved R, Saha S, Westlund B, Perier C, Burnam L, Sluder A, Hoener M, Rodrigues CMP, Alfonso A, Steer C, Liu L, Przedborski S, Wolozin B. 2005. Similar patterns of mitochondrial vulnerability and rescue induced by genetic

modification of alpha-synuclein, parkin, and DJ-1 in Caenorhabditis elegans. J Biol Chem 280(52):42655-42668.
Abstract: How genetic and environmental factors interact in Parkinson disease is poorly understood. We have now compared the patterns of vulnerability and rescue of Caenorhabditis elegans with genetic modifications of three different genetic factors implicated in Parkinson disease (PD). We observed that expressing alpha-synuclein, deleting parkin (K08E3.7), or knocking down DJ-1 (B0432.2) or parkin produces similar patterns of pharmacological vulnerability and rescue. C. elegans lines with these genetic changes were more vulnerable than nontransgenic nematodes to mitochondrial complex I inhibitors, including rotenone, fenperoximate, pyridaben, or stigmatellin. In contrast, the genetic manipulations did not increase sensitivity to paraquat, sodium azide, divalent metal ions (Fe(II) or Cu(II)), or etoposide compared with the nontransgenic nematodes. Each of the PD-related lines was also partially rescued by the antioxidant probucol, the mitochondrial complex II activator, D-beta-hydroxybutyrate, or the anti-apoptotic bile acid tauroursodeoxycholic acid. Complete protection in all lines was achieved by combining D-beta-hydroxybutyrate with tauroursodeoxycholic acid but not with probucol. These results show that diverse PD-related genetic modifications disrupt the mitochondrial function in C. elegans, and they raise the possibility that mitochondrial disruption is a pathway shared in common by many types of familial PD.

Veldman BAJ, Wijn AM, Knoers N, Praamstra P, Horstink Mwim. 1998. Genetic and environmental risk factors in Parkinson's disease. Clin Neurol Neurosurg 100(1):15-26.
Abstract: Parkinson's disease (PD) is a multifactorial disorder, caused by a combination of age, genetics and environmental factors. Nigral cells are susceptible to multiple causes of derangement of normal cell function, all of which may contribute to the same Parkinson phenotype. Autosomal dominant alpha-synuclein-gene PD represents one of the pure genetic forms, whereas cases of sporadic PD probably depend more on age and environmental factors, MPTP-Parkinsonism being the purest example of an environmentally caused Parkinson phenotype. This review suggests that pesticides-herbicides; smoking and head trauma probably represent the most eligible candidates for environmental factors involved in provoking PD or influencing its natural course. (C) 1998 Elsevier Science B.V. All rights reserved.

Vidal JS, Elbaz A, Clavel J, Delemotte B, Alperovitch A, Tzourio C. 2002. Exposure to pesticides and Parkinson's disease: A community-based, case-control study among a population characterized by a high prevalence of exposure. Mov Disord 17:S80-S81.

Vieregge P. 1997. Epidemiology of idiopathic Parkinson's disease. Nervenheilkunde 16(3):151-157.
Abstract: The prevalence of idiopathic Parkinson's disease (MP) in the industrialized countries of the Western hemisphere is about 120 to 150/10 (5). Age structure of the population under investigation is of paramount

importance for prevalence results. Recent follow-up studies do not support earlier contentions that MP prevalence is lower among the yellow-coloured populations of the Far East than in white populations in Europe or the USA. The data on prevalence in blacks are inconclusive. MP is obviously not age-associated, since the age-specific incidence curves do not steadily increase up to the highest age groups, but rather seem to fall after the eighth decade of life. Exposition to herbicides and organic solvents could build up a possible aetiologic clue in the future, since these variables are among the most frequent results linked to the presence of MP in various recent case-control studies. However, neither occupational risks nor dose-effect relations can be shown at present. The most stable result from ail case-control studies over the last three decades remains the enigmatic negative association of nicotine consumption prior to or during the disease.

Vieregge P. 2002. Pesticide exposure and Parkinson's syndrome - the epidemiological and experimental evidence. Nervenarzt 73(10):982-289. Abstract: Retrospective case-control studies among patients with idiopathic Parkinson's syndrome (IPS) show a positive association to the existence of a - mostly premorbid - exposure to pesticides. In acute pesticide intoxications, usually symptoms other than parkinsonism are found. Therefore, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) continues to be the agent best documented both experimentally and clinically to cause a clinical syndrome comparable to IPS. It is debated whether still unknown effects between exogenous pesticide exposure and the xenobiotic enzyme system may lead to IPS in single genetically susceptible individuals. In practice, the present data on the problem of pesticide exposure in IPS are irrelevant for medicolegal considerations.

Vieregge P, Vonmaravic C, Friedrich HJ. 1992. Life-style and dietary factors early and late in parkinsons-disease. Can J Neurol Sci 19(2):170-173. Abstract: The study investigated features of life-style and dietary habits early and late in life of patients with idiopathic Parkinson's disease (IPD). Seventy-one patients and 103 controls were interviewed personally with a structured questionnaire. Living in villages during primary school time was significantly more frequent among patients, and in the urban environment patients had lived less frequently in larger-sized towns. Mushroom harvesting during childhood was more frequent among patients. No difference between patients and controls was found in childhood water supply habits of fishing in the countryside or at the seaside, and eating such fish. Actual food preference in patients was greater for almonds and plums. while no difference was found in the actual intake of mushrooms, peanuts, oil-dressed salad, fish and animal offals. The study did not indicate a higher consumption of foods known to harbour heavy metals and pesticides in IPD patients either long before or during the disease. Reduced consumption of foodstuffs rich in vitamin E, as reported previously for premorbid patients, is no longer observed in patients with overt disease.

Virmani A, Gaetani F, Binienda Z. 2005 Aug. Effects of Metabolic Modifiers Such as Carnitines, Coenzyme Q10, and PUFAs against Different Forms of Neurotoxic Insults: Metabolic Inhibitors, MPTP, and Methamphetamine. Ann

N Y Acad Sci 1053:183-91 .
Abstract: A number of strategies using the nutritional approach are emerging for the protection of the brain from damage caused by metabolic toxins, age, or disease. Neural dysfunction and metabolic imbalances underlie many diseases, and the inclusion of metabolic modifiers may provide an alternative and early intervention approach that may prevent further damage. Various models have been developed to study the impact of metabolism on brain function. These have also proven useful in expanding our understanding of neurodegeneration processes. For example, the metabolic compromise induced by inhibitors such as 3-nitropropionic acid (3-NPA), rotenone, and 1-methyl-4-phenylpyridinium (MPP(+)) can cause neurodegeneration in animal models and these models are thought to simulate the processes that may lead to diseases such as Huntington's and Parkinson's diseases. These inhibitors of metabolism are thought to selectively kill neurons by inhibiting various mitochondrial enzymes. However, the eventual cell death is attributed to oxidative stress damage of selectively vulnerable cells, especially highly differentiated neurons. Various studies indicate that the neurotoxicity resulting from these types of metabolic compromise is related to mitochondrial dysfunction and may be ameliorated by metabolic modifiers such as l-carnitine (L-C), creatine, and coenzyme Q10, as well as by antioxidants such as lipoic acid, vitamin E, and resveratrol. Mitochondrial function and cellular metabolism are also affected by the dietary intake of essential polyunsaturated fatty acids (PUFAs), which may regulate membrane composition and influence cellular processes, especially the inflammatory pathways. Cellular metabolic function may also be ameliorated by caloric restriction diets. L-C is a naturally occurring quaternary ammonium compound that is a vital cofactor for the mitochondrial entry and oxidation of fatty acids. Any factors affecting L-C levels may also affect ATP levels. This endogenous compound, L-C, together with its acetyl ester, acetyl-l-carnitine (ALC), also participates in the control of the mitochondrial acyl-CoA/CoA ratio, peroxisomal oxidation of fatty acids, and production of ketone bodies. A deficiency of carnitine is known to have major deleterious effects on the CNS. We have examined L-C and its acetylated derivative, ALC, as potential neuroprotective compounds using various known metabolic inhibitors, as well as against drugs of abuse such as methamphetamine.

Vitvitsky V, Mosharov E, Tritt M, Ataullakhanov F, Banerjee R. 2003. Redox regulation of homocysteine-dependent glutathione synthesis. Redox Report 8(1):57-63.
Abstract: In certain tissues, glutathione biosynthesis is connected to methionine metabolism via the trans-sulfuration pathway. The latter condenses homocysteine and serine to cystathionine in a reaction catalyzed by cystathionine beta-synthase followed by cleavage of cystathionine to cysteine and alpha-ketoglutarate by gamma-cystathionase. Cysteine is the limiting amino acid in glutathione biosynthesis, and studies in our laboratory have shown that approximately 50% of the cysteine in glutathione is derived from homocysteine in human

liver cells. In this study, we have examined the effect of pro- and antioxidants on the flux of homocysteine through the trans-sulfuration pathway in the human hepatoma. cell line, HepG2. Our studies reveal that pyrrolidine dithiocarbamate and butylated hydroxyanisole enhance the flux of homocysteine through the trans-sulfuration pathway as has been observed previously with the pro-oxidants, H2O2 and tertiary butyl hydroperoxide. In contrast, antioxidants such as catalase, superoxide dismutase and a water-soluble derivative of vitamin E elicit the opposite effect and result in diminished flux of homocysteine through the trans-sulfuration pathway. These studies provide the first evidence for the reciprocal sensitivity of the trans-sulfuration pathway to pro- and antioxidants, and demonstrate that the upstream half of the glutathione biosynthetic pathway (i.e. leading to cysteine biosynthesis) is redox sensitive as is the regulation of the well-studied enzymes in the downstream half (leading from cysteine to glutathione), namely, gamma-glutamyl-cysteine ligase and glutathione synthetase.

Wajsbort J, Youdim MB. 1984. A new selective suicide inhibitor of peripheral DOPA decarboxylase. Adv Neurol 40:251-8.
Abstract: Although the present study is based on a small number of patients, our clinical data clearly show that DFMD is as effective as other peripheral decarboxylase inhibitors in potentiating the action of L-DOPA. In 3 patients, we observed an improvement above that with previous therapy. This may suggest that in some patients DFMD is either more effective than other decarboxylase inhibitors or that it has its own effect. Subjective complaints with DFMD were frequent and 9 of the 10 patients preferred their previous therapy. In 5 patients, we observed an increase in blood pressure while on DFMD plus L-DOPA and 2 had EEG changes. These effects appear to be drug-related. Because of its side effects, DFMD cannot be considered in this form as a useful adjuvant in Parkinson therapy. However, further studies are necessary for the development of selective inhibitors.

Waldmeier PC. 2003. Prospects for antiapoptotic drug therapy of neurodegenerative diseases. Progress in Neuro-Psychopharmacology & Biological Psychiatry 27(2):303-321.
Abstract: The evidence for a role of apoptosis in the neurodegenerative diseases, Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), and in the more acute conditions of cerebral ischemia, traumatic brain injury (TBI), and spinal cord injury (SCI) is reviewed with regard to potential intervention by means of small antiapoptotic molecules. In addition, the available animal models for these diseases are discussed with respect to their relevance for testing small antiapoptotic molecules in the context of what is known about the apoptotic pathways involved in the diseases and the models. The principal issues related to pharmacotherapy by apoptosis inhibition, i.e., functionality of rescued neurons and potential interference with physiologically occurring apoptosis, are pointed out. Finally, the properties of a number of small antiapoptotic molecules currently under clinical investigation are summarized. It is concluded that the evidence for a role of apoptosis at

present is more convincing for PD and ALS than for AD. In PD, damage to dopaminergic neurons may occur through oxidative stress and/or mitochondrial impairment and culminate in activation of an apoptotic, presumably p53-dependent cascade; some neurons experiencing energy failure may not be able to complete apoptosis, end up in necrosis and give rise to inflammatory processes. These events are reasonably well reflected in some of the PD animal models, notably those involving I methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone. In sporadic ALS, an involvement of pathways involving p53 and Bcl-2 family members appears possible if not likely, but is not established. The issue is important for the development of antiapoptotic compounds for the treatment of this disease because of differential involvement of p53 in different mutant superoxide dismutase (SOD) mice. Most debated is the role of apoptosis in AD; this implies that little is known about potentially involved pathways. Moreover, there is a lack of suitable animal models for compound evaluation. Apoptosis or related phenomena are likely involved in secondary cell death in cerebral ischemia, TBI, and SCI. Most of the pertinent information comes from animal experiments, which have provided some evidence for prevention of cell death by antiapoptotic treatments, but little for functional benefit. Much remains to be done in this area to explore the potential of antiapoptotic drugs. There is a small number of antiapoptotic compounds in clinical development. With some of them, evidence for maintenance of functionality of the rescued neurons has been obtained in some animal models, and the fact that they made it to phase 11 studies in patients suggests that interference with physiological apoptosis is not an obligatory problem. The prospect that small antiapoptotic molecules will have an impact on the therapy of neurodegenerative diseases, and perhaps also of ischemia and trauma, is therefore judged cautiously positively. 

Waldmeier PC, Boulton AA, Cools AR, Kato AC, Tatton WG. 2000. Neurorescuing effects of the GAPDH ligand CGP 3466B. J Neural Transm Suppl (60): 197-214.

Abstract: (-)-Deprenyl, used for the treatment of Parkinson's disease, was reported to possess neurorescuing/antiapoptotic effects independent of its MAO-B inhibiting properties. It is metabolized to (-)-desmethyldeprenyl, which seems to be the active principle, and further to (-)-amphetamine and (-)-methamphetamine, which antagonize its rescuing effects. These complications may explain the limited neurorescuing potential of (-)-deprenyl observed clinically. CGP 3466 (dibenzo[b,f]oxepin-10-ylmethyl-methyl-prop-2-ynyl-amine), structurally related to (-)-deprenyl, exhibits virtually no MAO-B nor MAO-A inhibiting properties and is not metabolized to amphetamines. It was shown to bind to glyceraldehyde-3-phosphate dehydrogenase, a glycolytic enzyme with multiple other functions including an involvement in apoptosis, and shows neurorescuing properties qualitatively similar to, but about 100-fold more potent than those of (-)-deprenyl in several in vitro and in vivo paradigms. In concentrations ranging from 10(-13)-10(-5) M, it rescues partially differentiated PC12 cells

from apoptosis induced by trophic withdrawal, cerebellar granule cells from apoptosis induced by cytosine arabinoside, rat embryonic mesencephalic dopaminergic cells from death caused by MPP+, and PAJU human neuroblastoma cells from death caused by rotenone. However, it did not affect apoptosis elicited by a variety of agents in rapidly proliferating cells from thymus or skin or in liver or kidney cells. In vivo, it rescued facial motor neuron cell bodies in rat pups after axotomy, rat hippocampal CA1 neurons after transient ischemia/hypoxia, and mouse nigral dopaminergic cell bodies from death induced by MPTP, in doses ranging between 0.0003 and 0.1 mg/kg p.o. or s.c., depending on the model. It also partially prevented the loss of tyrosine hydroxylase immunoreactivity in the substantia nigra of 6-OHDA-lesioned rats and improved motor function in these animals. Moreover, it prolonged the life-span of progressive motor neuronopathy (pmn) mice (a model for ALS), preserved their body weight and improved their motor performance. This was accompanied by a decreased loss of motor neurons and motor neuron fibers, and protection of mitochondria. The active concentration- or dose-ranges in the different in vitro and in vivo paradigms were remarkably similar. In several paradigms, bell-shaped dose-response curves were observed, the rescuing effect being lost above about 1 mg/kg, a fact that must be considered in clinical investigations.

Walkinshaw G, Waters CM. 1994. Neurotoxin-induced cell-death in neuronal pc12 cells is mediated by induction of apoptosis. Neuroscience 63(4):975-987. Abstract: Death of neuronal cells during development and following deprivation of trophic factors is known to occur via an active mechanism requiring RNA and protein synthesis, known as apoptosis. Apoptosis is a form of cell ''suicide'' whereby the cell decides its own fate by activating a genetic programme of cell death. In contrast, necrosis is a passive uncontrolled form of cell death often observed in response to a toxic insult. Although it is known that neuronal cell death during development occurs by apoptosis, the mechanisms underlying neurotoxin-induced neuronal cell death remain poorly understood. In this study we have examined the mechanism by which 6-hydroxydopamine, a specific neurotoxin for catecholaminergic cells, induces neuronal cell death in in vitro. We report that 6-hydroxydopamine induces cell death in the neuronal PC12 cell line via a mechanism which has the characteristic morphological and biochemical hallmarks of apoptosis. PC12 cells induced to die by 6-hydroxydopamine treatment exhibited cell shrinkage. classical chromatin condensation and membrane blebbing. Analysis of DNA integrity from 6-hydroxydopamine-treated cells revealed cleavage of DNA into regular sized fragments, a biochemical hallmark of apoptosis. 6-Hydroxydopamine-induced apoptosis of PC12 cells was suppressed by desipramine, a monoamine uptake inhibitor, suggesting that 6-hydroxydopamine is initiating apoptosis via a specific intracellular mechanism. Aurintricarboxylic acid, a general inhibitor of nucleases. also suppressed 6-hydroxydopamine-induced apoptosis, suggesting the involvement of an endonuclease in the death pathway. The aetiology of idiopathic Parkinson's disease remains uncertain. although evidence

suggests that endogenous and/or exogenous toxins may initiate neuronal cell death in this disease. The dopaminergic neurotoxin 6-hydroxydopamine is used to generate animal models of Parkinson's disease in vivo. We have demonstrated that this neurotoxin kills neuronal cells in vitro by an active process of apoptosis. Thus, the possibility exists that cell death in neurodegenerative diseases such as Parkinsonism also occurs in an active manner initiated by as yet unidentified environmental or metabolic toxins. Cell death that involves activation of an apoptotic programme can be modulated by addition of extracellular trophic factors, and is also controlled by the levels of intracellular factors. If neurotoxin-induced apoptosis plays a role in Parkinson's disease the implication is that the neuronal degeneration may be prevented by pharmacological manipulations.

Wallace MA, Bailey S, Fukuto JM, Valentine JS, Gralla EB. 2005. Induction of phenotypes resembling CuZn-superoxide dismutase deletion in wild-type yeast cells: An in vivo assay for the role of superoxide in the toxicity of redox-cycling compounds. Chem Res Toxicol 18(8):1279-1286. Abstract: Yeast (Saccharomyces cerevisiae) lacking the enzyme CuZn-superoxide dismutase (sod1 Delta) display a large number of dioxygen sensitive phenotypes, such as amino acid auxotrophies, sensitivity to elevated temperatures, and sensitivity to 100% dioxygen, which are attributed to superoxide stress. Such cells are exquisitely sensitive to small amounts of the herbicide paraquat (methyl viologen), which is known to produce high fluxes of superoxide in vivo via a redox-cycling mechanism. We report that dioxygen sensitive phenotypes similar to those seen in sod1 Delta cells can be induced in wild-type cells by treatment with moderate concentrations of paraquat or diquat, another bipyridyl herbicide, providing strong evidence that the mechanism of toxicity for both of these compounds is attributable to superoxide stress. Certain redox-cycling quinone compounds (e.g., menadione and plumbagin) are also far more toxic toward sod1 Delta than to wild type. However, treatment of wild-type yeast with menadione or plumbagin did not induce sod1 Delta-like phenotypes, although toxicity was evident. Thus, their toxicity in wild type cells is predominantly, but not exclusively, due to mechanisms unrelated to superoxide production. Further evidence for a different basis of toxicity toward wild-type yeast in these two classes of redox-cycling compounds includes the observations that W growth in low oxygen alleviated the effects of paraquat and diquat but not those of menadione or plumbagin and (ii) activity of the superoxide sensitive enzyme aconitase is affected by very low concentrations of paraquat but only by higher, growth inhibitory concentrations of menadione. These results provide the basis for an easy qualitative assay of the contribution of redox-cycling to the toxicity of a test compound. Using this method, we analyzed the Parkinsonism-inducing compound 1-methyl-4-phenylpyridinium and found that redox cycling and superoxide toxicity are not the predominant factor in its toxic mechanism.

Walters TL, Irwin I, Delfani K, Langston JW, Janson AM. 1999. Diethyldithiocarbamate causes nigral cell loss and dopamine depletion with nontoxic doses of MPTP. Exp Neurol 156(1):62-70.

Abstract: Although nontoxic when administered alone, diethyldithiocarbamate (DDC) is known to enhance the dopamine-depleting effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the mouse striatum. The purpose of the present study was twofold: (i) to carefully characterize the effects of DDC on MPTP-induced degeneration of dopaminergic neurons in substantia nigra pars compacts using unbiased, stereological cell counting techniques and (ii) to determine whether or not DDC can convert a nontoxic dose of MPTP into one which is clearly toxic on dopaminergic neurons in the substantia nigra. A single low dose of MPTP (15 mg/kg intraperitoneally (ip)) was used for these studies, which failed to induce any neurochemical or histological effects on the nigrostriatal system of C57BL/6 mice when administered alone. However, when animals were pretreated with DDC (400 mg/kg ip), the same dose of MPTP resulted in a 50% loss of neurons in the substantia nigra pars compacta, as well as a 70% reduction in striatal dopamine (DA). A 31% reduction of DA in the ventral mesencephalon was also seen. This combined regimen of DDC and MPTP was not significantly different from a maximally tolerated "toxic" dose of MPTP alone (15 mg/kg x 4, 1 h apart, ip). As expected, animals receiving DDC alone did not show any dopamine depletion nor nigral neuronal loss. The present study confirms previous work suggesting that DDC enhances MPTP-induced nigral cell loss and shows for the first time that DDC can "unmask" MPTP toxicity. These observations could have implications for theories on the cause of Parkinson's disease. (C) 1999 Academic Press.

Wang C, Ko HS, Thomas B, Tsang F, Chew KCM, Tay SP, Ho MWL, Lim TM, Soong TW, Pletnikova O, Troncoso J, Dawson VL, Dawson TM, Lim KL. 2005. Stress-induced alterations in parkin solubility promote parkin aggregation and compromise parkin's protective function. Hum Mol Genet 14(24): 3885-3897.
Abstract: Mutations in parkin are currently recognized as the most common cause of familial Parkinsonism. Emerging evidence also suggests that parkin expression variability may confer a risk for the development of the more common, sporadic form of Parkinson's disease (PD). Supporting this, we have recently demonstrated that parkin solubility in the human brain becomes altered with age. As parkin apparently functions as a broad-spectrum neuroprotectant, the resulting decrease in the availability of soluble parkin with age may underlie the progressive susceptibility of the brain to stress. Interestingly, we also observed that many familial-PD mutations of parkin alter its solubility in a manner that is highly reminiscent of our observations with the aged brain. The converging effects on parkin brought about by aging and PD-causing mutations are probably not trivial and suggest that environmental modulators affecting parkin solubility would increase an individual's risk of developing PD. Using both cell culture and in vivo models, we demonstrate here that several PD-linked stressors, including neurotoxins (MPP+, rotenone, 6-hydroxydopamine), paraquat, NO, dopamine and iron, induce alterations in parkin solubility and result in its intracellular aggregation. Furthermore, the depletion of soluble, functional forms of parkin is associated with reduced proteasomal activities

and increased cell death. Our results suggest that exogenously introduced stress as well as endogenous dopamine could affect the native structure of parkin, promote its misfolding, and concomitantly compromise its protective functions. Mechanistically, our results provide a link between the influence of environmental and intrinsic factors and genetic susceptibilities in PD pathogenesis.

Wang FL, Semchuk KM, Love EJ. 1994. Reliability of environmental and occupational exposure data provided by surrogate respondents in a case-control study of parkinsons-disease. J Clin Epidemiol 47(7):797-807. Abstract: This study used data provided by 40 non-demented Parkinson's disease patients and 101 community controls, and by their 110 spouses and 31 adult children to assess the reliability of surrogate-provided rural environmental and occupational exposure information on the index subjects. The level of overall raw agreement between the index subjects and the spouse or adult child surrogates varied from 50.0 to 100.0% for the case-surrogate group and from 80.6 to 96.0% for the control-surrogate group. We did not detect significant differences in overall raw agreement between the case-surrogate and control-surrogate groups or between the spouse-surrogate and adult child-surrogate groups, for any of the variables studied. Considering all index subjects and their surrogates, the level of overall raw agreement was 80.3% for well water consumption, 82.3% for farm living, 85.8% for agricultural work, 87.1% for use of pesticides, 87.9% for field crop farming and 91.9% for use of fertilizers. However, the kappa estimates were lower, varying from 0.48 (SE = 0.20) for fertilizer use to 0.66 (SE = 0.11) for crop farming. The level of specific agreement was 52.2% for fertilizer use, 64.0% for pesticide use, 71.4% for agricultural work, 73.9% for crop farming, 80.9% for farm living, and 83.6% for well water consumption. The overall findings of this study support the use, if necessary, of spouses and adult children of index subjects as surrogate respondents in case-control studies of rural environmental and occupational exposures and Parkinson's disease and, possibly, other neurologic diseases. Specific agreement seems to be a better index of reliability than overall agreement in studies where exposure is rare.

Wang G, Qi C, Fan GH, Zhou HY, Chen SD. 2005. PACAP protects neuronal differentiated PC12 cells against the neurotoxicity induced by a mitochondrial complex I inhibitor, rotenone. FEBS Lett 579(18):4005-4011. Abstract: In vivo and in vitro studies have suggested a neuroprotective role for Pituitary adenylate cyclase activating polypeptide (PACAP) against neuronal insults. Here, we showed that PACAP27 protects against neurotoxicity induced by rotenone, a mitochondrial complex I inhibitor that has been implicated in the pathogenesis of Parkinson's disease (PD). The neuroprotective effect of PACAP27 was dose-dependent and blocked by its specific receptor antagonist, PACAP6-27. The effects of PACAP27 on rotenone-induced cell death were mimicked by dibutyryl-cAMP (db-cAMP), forskolin and prevented by the PKA inhibitor H89, the ERK inhibitor PD98059 and the p38 inhibitor SB203580. PACAP27 administration blocked rotenone-induced increases in the level of caspase-3-like activity, whereas

could not restore mitochondrial activity damaged by rotenone. Thus, our results demonstrate that PACAP27 has a neuroprotective role against rotenone-induced neurotoxicity in neuronal differentiated PC12 cells and the neuroprotective effects of PACAP are associated with activation of MAP kinase pathways by PKA and with inhibition of caspase-3 activity; the signaling mechanism appears to be mediated through mitochondrial-independent pathways. (c) 2005 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

Wang X, Qin ZH, Leng Y, Wang Y, Jin X, Chase TN, Bennett MC. 2002 Dec. Prostaglandin A1 inhibits rotenone-induced apoptosis in SH-SY5Y cells. J Neurochem 83(5):1094-102.
Abstract: The degeneration of nigral dopamine neurons in Parkinson's disease (PD) reportedly involves a defect in brain mitochondrial complex I in association with the activation of nuclear factor-kappaB (NF-kappaB) and caspase-3. To elucidate molecular mechanisms possibly linking these events, as well as to evaluate the neuroprotective potential of the cyclopentenone prostaglandin A1 (PGA1), an inducer of heat shock proteins (HSPs), we exposed human dopaminergic SH-SY5Y cells to the complex I inhibitor rotenone. Dose-dependent apoptosis was preceded by the nuclear translocation of NF-kappaB and then the activation of caspase-3 over the ensuing 24 h. PGA1 increased the expression of HSP70 and HSP27 and protected against rotenone-induced apoptosis, without increasing necrotic death. PGA1 blocked the rotenone-induced nuclear translocation of NF-kappaB and attenuated, but did not abolish, the caspase-3 elevation. Unexpectedly, the caspase-3 inhibitor, Ac-DEVD.CHO (DEVD), at a concentration that completely prevented the caspase-3 elevation produced by rotenone, failed to protect against apoptosis. These results suggest that complex I deficiency in dopamine cells can induce apoptosis by a process involving early NF-kappaB nuclear translocation and caspase-3 activation. PGA1 appears to protect against rotenone-induced cell death by inducing HSPs and blocking nuclear translocation of NF-kappaB in a process that attenuates caspase-3 activation, but is not mediated by its inhibition.

Wang XH, Xu HX. 2005. Possible involvement of Ca2+ signaling in rotenone-induced apoptosis in human neuroblastorna SH-SY5Y cells. Neurosci Lett 376(2): 127-132.
Abstract: Rotenone, an inhibitor of mitochondrial respiratory chain complex 1, is a useful tool to elicit animal model of Parkinson's disease. Rotenone-induced neuronal apoptosis may contribute to the etiology of Parkinson's disease. However, the mechanism of rotenone-induced apoptosis is not fully understood. In the present study, we show that Ca2+ signaling is essential for rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells. By using Fluo-3/AM and Fura-2/AM, the fluorescent calcium indicator, rotenone was found to cause a rise in intracellular free Ca2+ ([Ca2+](i)). The intracellular Ca2+ chelator BAPTA attenuated rotenone-induced apoptosis. Notably, Ca2+ suppression also prevented rotenone-induced apoptotic related events including reactive oxygen species production, G2/M cell cycle arrest and caspase activation, suggesting that Ca2+ signaling

is upstream to these events. In the absence of extracellular Ca2+, the rotenone-induced [Ca2+], elevation was inhibited. Further, the voltage-dependent Ca2+ channel blocker nifedipine suppressed most of the elevation of [Ca2+](i) induced by rotenone. These results demonstrate that rotenone leads to an elevation in [Ca2+](i) through Ca2+ influx by the opening of voltage-gated Ca2+ channel. This study of rotenone may help to elucidate the neurodegenerative mechanisms in Parkinson's disease. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Wang XX, Qin ZH, Leng Y, Wang YM, Jin XN, Chase TN, Bennett MC. 2002. Prostaglandin A(1) inhibits rotenone-induced apoptosis in SH-SY5Y cells. J Neurochem 83(5):1094-1102.
Abstract: The degeneration of nigral dopamine neurons in Parkinson's disease (PD) reportedly involves a defect in brain mitochondrial complex I in association with the activation of nuclear factor-kappaB (NF-kappaB) and caspase-3. To elucidate molecular mechanisms possibly linking these events, as well as to evaluate the neuroprotective potential of the cyclopentenone prostaglandin A(1) (PGA(1)), an inducer of heat shock proteins (HSPs), we exposed human dopaminergic SH-SY5Y cells to the complex I inhibitor rotenone. Dose-dependent apoptosis was preceded by the nuclear translocation of NF-kappaB and then the activation of caspase-3 over the ensuing 24 h. PGA(1) increased the expression of HSP70 and HSP27 and protected against rotenone-induced apoptosis, without increasing necrotic death. PGA(1) blocked the rotenone-induced nuclear translocation of NF-kappaB and attenuated, but did not abolish, the caspase-3 elevation. Unexpectedly, the caspase-3 inhibitor, Ac-DEVD.CHO (DEVD), at a concentration that completely prevented the caspase-3 elevation produced by rotenone, failed to protect against apoptosis. These results suggest that complex I deficiency in dopamine cells can induce apoptosis by a process involving early NF-kappaB nuclear translocation and caspase-3 activation. PGA, appears to protect against rotenone-induced cell death by inducing HSPs and blocking nuclear translocation of NF-kappaB in a process that attenuates caspase-3 activation, but is not mediated by its inhibition.

Wastensson G, Hagberg S, Andersson E, Johnels B, Barregard L. 2006 Jan. Parkinson's disease in diphenyl-exposed workers-A causal association? Parkinsonism Relat Disord 12(1):29-34.
Abstract: We report a cluster of five cases of Parkinson's disease (PD) among paper mill workers exposed to a fungicide, diphenyl. The cause of PD is still unknown, but epidemiological studies have indicated an elevated risk of developing PD after exposure to pesticides. The five cases of PD were found in a group of 255 diphenyl-exposed workers, and the number of expected cases in the exposed group was estimated to be 0.9, resulting in a relative risk of 5.6 (95% CI 1.8-13). Exposure to diphenyl may have contributed to this PD cluster, but chance is an alternative explanation.

Watabe M, Nakaki T. 2004. Rotenone induces apoptosis via activation of bad in human dopaminergic SH-SY5Y cells. J Pharmacol Exp Ther 311(3): 948-953.

Abstract: Chronic complex I inhibition caused by rotenone induces features of Parkinson's disease in rats, including selective nigrostriatal dopaminergic degeneration and Lewy bodies with alpha-synuclein-positive inclusions. To determine the mechanisms underlying rotenone-induced neuronal death, we used an in vitro model of human dopaminergic SH-SY5Y cells. In rotenone-induced cell death, rotenone induced Bad dephosphorylation without changing the amount of Bad proteins. Rotenone also increased the amount of alpha-synuclein in cells showing morphological changes in response to rotenone. Because Bad and alpha-synuclein are known to bind to 14-3-3 proteins, we examined the effects of rotenone on these complexes. Whereas a decreased Bad amount bound to 14-3-3 proteins, rotenone increased alpha-synuclein binding to these proteins. Beccause dephosphorylation by calcineurin activates Bad, we examined the possible involvement of Bad activation in rotenone-induced apoptosis by using the calcineurin inhibitor tacrolimus (FK506). Tacrolimus suppressed two rotenone-induced actions: Bad dephosphorylation and apoptosis. Furthermore, the inhibition of caspase-9, which functions downstream from Bad, completely suppressed rotenone-induced apoptosis. Our findings demonstrate that Bad activation plays a role in rotenone-induced apoptosis of SH-SY5Y cells.

Wechsler LS, Checkoway H, Franklin GM, Costa LG. 1991. A pilot-study of occupational and environmental risk-factors for parkinsons-disease. Neurotoxicology 12(3):387-392.
Abstract: Increasingly, the etiology of Parkinson's disease (PD) has been linked to exposures to environmental toxicants. This epidemiologic pilot study used a self-administered questionnaire among 34 PD cases and 22 other neurology clinic control patients. All subjects were at least 40 years old. Risk factors investigated included occupation, well-water use, pesticide use, metal exposures, medical history, smoking, alcohol consumption, and drug use. Twenty-six percent of the male PD cases reported having been employed in farming versus eleven percent for male controls (OR = 3.1, 95%, C.L = 0.3 to 35). Sixteen percent of male cases versus none of the controls reported employment as welders. No clear trends involving exposure to either occupational or home pesticides emerged. In assessing occupational exposures to metals, aluminum and copper exposures tended to be more common among male cases than male controls. Additionally, as reported in other studies, smoking showed an inverse relationship with PD. Although the findings reported here are provocative, these results are statistically imprecise and must be interpreted cautiously because of the small number of subjects included in the study.

Weinstock M, Gorodetsky E, Poltyrev T, Gross A, Sagi Y, Youdim M. 2003. A novel cholinesterase and brain-selective monoamine oxidase inhibitor for the treatment of dementia comorbid with depression and Parkinson's disease. Progress in Neuro-Psychopharmacology & Biological Psychiatry 27 (4):555-561.
Abstract: Degeneration of cholinergic cortical neurons is one of the main reasons for the cognitive deficit in dementia of the Alzheimer type (AD) and in dementia with Lewy bodies (DLB). Many subjects with AD and DLB

have extrapyramidal dysfunction and depression resulting from degeneration of dopaminergic, noradrenergic and serotoninergic neurons. We prepared a novel drug, TV-3326 (N-propargyl-3R-aminoindan-5yl)-ethyl methylcarbamate), with both cholinesterase (ChE) and monoamine oxidase (MAO) inhibitory activity, as potential treatment of AD and DLB. TV-3326 inhibits brain acetyl and butyrylcholinesterase (BuChE) in rats after oral doses of 10-100 mg/kg. After chronic but not acute treatment, it inhibits MAO-A and -B in the brain by more than 70% but has almost no effect on these enzymes in the small intestine in rats and rabbits. The brain selectivity results in minimal potentiation of the pressor response to oral tyramine. TV-3326 acts like other antidepressants in the forced swim test in rats, indicating a potential for antidepressant activity. Chronic treatment of mice with TV-3326 (26 mg/kg) prevents the destruction of nigrostriatal neurons by the neurotoxin MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). In addition to ChE and MAO inhibition, the propargylamine moiety of TV-3326 confers neuroprotective activity against cytotoxicity induced by ischemia and peroxynitrite in cultured neuronal cells that results from prevention of the fall in mitochondrial membrane potential and antiapoptotic activity. These unique multiple actions of TV-3326 make it a potentially useful drug for the treatment of dementia with Parkinsonian-like symptoms and depression. (C) 2003 Elsevier Science Inc. All rights reserved.

Weiss B. 2000. Vulnerability to pesticide neurotoxicity is a lifetime issue. Neurotoxicology 21(1-2):67-73.
Abstract: Early development is not the only life stage during which which we see intensified responses to the adverse effects of chemicals. Vulnerability to toxic processes rises again late in life, and in many ways recapitulates the imperfect defenses deployed by the immature organism. One feature common to both early and late phases is a reduced capacity to compensate for impairment. In the first case, the functional mechanisms have yet to evolve. In the second, they have passed into what might be called a post-mature decline. Traced across the life cycle, this progression might be depicted as an inverted U. The developing brain, however, is equipped with immense plastic potential; the aging brain has lost much of its plasticity. The altered function of the aging brain, however, is not simply an outcome of how long the organism has lived. "Aging" is not a mechanistic explanation. Events occurring during life must account for the changes. Older brains are already high-maintenance properties, so that exposure to substances with neurotoxic properties, such as pesticides, may accelerate the process, or exploit its dwindling capacities to resist their effects. From this vantage point, toxicants can act in three ways to depress function during advanced age: they may interfere with brain development, leaving a legacy of diminished redundancy not apparent until it is further compromised during aging; they may hasten the progressive erosion of function observed with certain abilities; they may exert greater effects in the aging brain because the aging nervous system has already undergone a reduction in its ability to withstand toxic challenges. (C) 2000 Inter Press, Inc.

WEIST HJ. 1957. [Toxic parkinsonism with Quarelli syndrome & cardiovascular disorders after chronic carbon disulfide poisoning.]. Arch Gewerbepathol Gewerbehyg 15(6):542-52.

Werneck ALD, Alvarenga H. 1999. Genetics, drugs and environmental factors in Parkinson's disease - A case-control study. Arq Neuropsiquiatr 57(2B): 347-355.
Abstract: A case-control study of Parkinson's disease (PD) was conducted in the city of Rio de Janeiro based on the assumption that neurotoxins with secondary parkinsonian action may be related to the development of Parkinson's disease. Ninety-two subjects with PD and 110 controls were queried through a questionnaire in order to investigate possible risk factors for the disease. The following factors were studied: herbicides/pesticides, exposure to chemicals, ingestion of drugs with secondary PD effects, rural life, water well source, family history, cranial trauma and cigarette smoking. Study of mentioned factors was achieved through univariate, stratified and multivariate analyses. Univariate and multivariate analyses demonstrated that PD was positively associated with family history (OR = 14.5; CI = 2.98 - 91.38), with the use of drugs with secondary PD action (OR = 11.01; CI = 3.41 - 39.41) and with exposure to chemical agents (OR = 5.87; CI = 1.48 - 27.23). PD was found to be inversely associated with cigarette smoking. (OR = 0.39; IC = 0.16 - 0.95). Stratified analysis only confirmed family history and drug use, besides demonstrating that cigarette consumption could be a protection factor, when aforementioned factors were involved. This study might be a warning as to the cares that need to be taken regarding drug use and occupational exposure to chemical agents, as both types of substances present secondary PD action.

Wesseling C, van Wendel de Joode B, Ruepert C, Leon C, Monge P, Hermosillo H, Partanen TJ. 2001 Oct-Dec. Paraquat in developing countries. Int J Occup Environ Health 7(4):275-86.
Abstract: The herbicide paraquat is considered safe by industry and the bulk of regulators worldwide. However, determinants of exposure from 30 years ago persist in developing countries. Little is known about systemic absorption from occupational exposures. The relationships between exposure determinants, levels of external exposure, biomarkers of exposure, and outcomes are not clear. High rates of severe acute poisonings have been documented. In addition, topical injuries occur in as many as 50% of exposed workers. Non-worker populations are also at risk, particularly children. Long-term and delayed health effects include Parkinson's disease, lung effects, and skin cancer. Regulatory agencies have not fully recognized either the inherent toxicity of paraquat or the particular risks derived from exposures in developing countries. Independent risk assessment in the developing-country context and application of the precautionary principle are necessary to prevent adverse effects of dangerous pesticides in susceptible populations.

Widdowson PS, Farnworth MJ, Upton R, Simpson MG. 1996. No changes in behaviour, nigro-striatal system neurochemistry or neuronal cell death following toxic multiple oral paraquat administration to rats. Human &

Experimental Toxicology 15(7):583-591.
Abstract: We have examined whether the widely used herbicide, paraquat (1,1'-dimethyl-4,4'dipyridylium) may accumulate in rat brain following multiple oral dosing (5 mg paraquat ion/kg/day) for 14 days and whether this dosing regime may produce signs of neurotoxicity. This dosing regime may determine whether low dose exposure to mammals may be neurotoxic. Using [C-14]paraquat to measure tissue and plasma paraquat concentrations, we observed significantly higher plasma and tissue paraquat concentrations in brain, liver, lungs and kidneys of rats which received multiple doses for 14 days, as compared to paraquat concentrations in tissues of rats which received only a single paraquat dose. Brain paraquat concentrations measured 24 h after dosing were tenfold higher in rats receiving 14 daily oral doses of paraquat, as compared to concentrations following a single oral dose. A neuropathological study of the rat brain yielded no evidence that multiple paraquat dosing resulted in neuronal cell damage. particular attention was paid to the nigrostriatal system. The paraquat treated rats gained approximately 10% less body weight over the 15 day experimental period as compared with controls demonstrating that the dose of paraquat was toxic to the animals. Measurements of locomotor activity using open field tests or activity monitors did not reveal any statistically significant differences between control animals and those receiving paraquat. Fore- and hind-limb grip strength were not significantly different between the paraquat treated and control rats at any time point during the dosing regime, nor was there any evidence for locomotor coordination deficits in any of the animals receiving paraquat. Densities of dopamine D1 and D2, MM)A, muscarinic and benzodiazepine receptors in the cerebral cortex and striatum were not significantly different between controls and rats which had received multiple paraquat doses. Concentrations of catecholamine neurotransmitters in the striatum, hypothalamus and frontal cerebral cortex were also measured to examine whether there was evidence for catecholamine depletion in these brain regions. We did not observe any significant reductions in dopamine, noradrenaline or DOPAC concentrations in any brain region of paraquat treated rats as compared with controls. On the contrary, dopamine concentrations in the striatim were significantly elevated in paraquat treated animals following a 15 day paraquat dosing regime. We attribute these changes in catecholamine concentrations to the general toxicity of paraquat which produces a stress response. In conclusion, we could not find any evidence that multiple paraquat dosing can lead to changes in locomotor activity or grip strength. In addition, the absence of neuropathology or changes in neurochemistry in the nigrostriatal tract demonstrates that paraquat does not behave like MPP+ (N-methyl-4-phenylpyridinium), the neurotoxic metabolite of MPTP

Wiley RG, Harrison MB, Levey AI, Lappi DA. 2003. Destruction of midbrain dopaminergic neurons by using immunotoxin to dopamine transporter. Cell Mol Neurobiol 23(4-5):839-850.
Abstract: 1. The ability to target specific neurons can be used to produce selective neural lesions and potentially to deliver therapeutically useful

moieties for treatment of disease. In the present study, we sought to determine if a monoclonal antibody to the dopamine transporter (anti-DAT) could be used to target midbrain dopaminergic neurons. 2. The monoclonal antibody recognizes the second, large extracellular loop of DAT. The antibody was conjugated to the "ribosome-inactivating protein"; saporin, and stereotactically pressure microinjected into either the center of the striatum or the left lateral ventricle of adult, male Sprague-Dawley rats. 3. Local intrastriatal injections produced destruction of dopaminergic neurons in the ipsilateral substantia nigra consistent with suicide transport of the immunotoxin. Intraventricular injections (i.c.v.) produced significant loss of dopaminergic neurons in the substantia nigra and ventral tegmental area bilaterally without evident damage to any other aminergic structures such as the locus coeruleus and raphe nuclei. To confirm the anatomic findings, binding of [H-3] mazindol to DAT in the striatum and midbrain was assessed using densitometric analysis of autoradiograms. Anti-DAT-saporin injected i.c.v. at a dose of 21 mug, but not 8 mug, produced highly significant decreases in mazindol binding consistent with loss of the dopaminergic neurons. 4. These results show that anti-DAT can be used to target midbrain dopaminergic neurons and that anti-DAT-saporin may be useful for producing a lesion very similar to the naturally occurring neural degeneration seen in Parkinson's disease. Anti-DAT-saporin joins the growing list of neural lesioning agents based on targeted cytotoxins.

Witholt R, Gwiazda RH, Smith DR. 2000. The neurobehavioral effects of subchronic manganese exposure in the presence and absence of pre-parkinsonism. Neurotoxicol Teratol 22(6):851-861.
Abstract: Recent studies have implicated chronic elevated exposures to environmental agents, such as metals (e.g., manganese, Mn) and pesticides, as contributors to neurological disease. In particular, there is a concern that sensitive subpopulations such as the aged may be at increased risk for the onset of neurologic disorders because elevated exposures to Mn is associated with increased incidence of parkinsonism. Here, we utilized a rat model of pre-parkinsonism to investigate the effects of Mn exposure on neurotoxicity and the exacerbation of parkinsonism. A pre-parkinsonism state was induced using a unilateral intrastriatal injection of 6-hydroxydopamine (6-OHDA), followed 4 weeks later by Mn exposure (4.8 mg Mn/kg x 3 intraperitoneal injections/week) for 5 weeks. Female Sprague-Dawley rats (n = 44) were divided among the following treatments: (A) control, saline/vehicle; (B) Mn only; (C) 6-OHDA only; and (D) 6-OHDA + Mn. Brain Mn levels were measured by ICP MS. Neurobehavioral function was assessed following Mn exposure using a functional observational battery (FOB) consisting of 10 neurobehavioral tests. Unilateral O-OHDA lesions produced significant ipsilateral vs, contralateral striatal dopamine depletions (60-70%), but no measurable impairment of neurobehavioral function, thereby substantiating this pre-parkinsonism (i.e., subthreshold) model. In contrast, Mn exposure resulted in significant impairment of neurobehavioral function for eight of the 10 FOE tests. No effects of Mn exposure on striatal dopamine depletion were detected, despite the 3.4-fold increase in brain Mn levels over controls.

Notably, Mn exposure in the presence of a pre-parkinsonism state significantly exacerbated the neurobehavioral impairment in the reactivity to handling (P < .049) and hopping contralateral rear limb ( P < .033) FOE tests. While the persistence and Mn dose - response relationship of these neurobehavioral effects were not evaluated here, these results nonetheless suggest that chronic Mn exposure may increase the risk of neurobehavioral impairment in subpopulations that are in a pre-parkinsonism state. (C) 2000 Elsevier Science Inc. All rights reserved.

Wong GF, Gray CS, Hassanein RS, Koller WC. 1991. Environmental risk-factors in siblings with parkinsons-disease. Arch Neurol 48(3):287-289.
Abstract: To investigate possible risk factors in Parkinson's disease, we conducted a case-controlled study of 19 families having two or more siblings with Parkinson's disease. Demographic data were collected, including lifetime histories of places of residence; sources of drinking water; occupations, such as farming; and exposure to herbicides and pesticides. Rural living and drinking well water, but not farming and herbicide exposure, were significantly increased in 38 parkinsonians compared with 38 normal control subjects. A comparison of parkinsonian siblings with siblings with essential tremor revealed no differences in any risk factors for the years of shared environment. These data suggest that living in a rural environment and drinking well water are risk factors for Parkinson's disease and that the total life exposure to an environmental toxin may be more important than exposure in early life.

Wood DM, Alsahaf H, Streete P, Dargan PI, Jones AL. 2005. Fatality after deliberate ingestion of the pesticide rotenone: a case report. Critical Care 9 (3):R280-R284.
Abstract: Rotenone is a pesticide derived from the roots of plants from the Leguminosae family. Poisoning following deliberate ingestion of these plant roots has commonly been reported in Papua New Guinea. However, poisoning with commercially available rotenone in humans has been reported only once previously following accidental ingestion in a 3.5-year-old child. Therefore, the optimal management of rotenone poisoning is not known. After deliberate ingestion of up to 200 ml of a commercially available 0.8% rotenone solution, a 47-year-old female on regular metformin presented with a reduced level of consciousness, metabolic acidosis and respiratory compromise. Metformin was not detected in premortem blood samples obtained. Despite intensive supportive management, admission to an intensive care unit, and empirical use of N-acetylcysteine and antioxidant therapy, she did not survive. Poisoning with rotenone is uncommon but is potentially fatal because this agent inhibits the mitochondrial respiratory chain. In vitro cell studies have shown that rotenone-induced toxicity is reduced by the use of N-acetylcysteine, antioxidants and potassium channel openers. However, no animal studies have been reported that confirm these findings, and there are no previous reports of attempted use of these agents in patients with acute rotenone-induced toxicity.

Woodward G. 2001. Autism and Parkinson's disease. Med Hypotheses 56(2):

246-249.
Abstract: The pathogenesis of Parkinson's disease, a neurodegenerative disorder, is multifaceted, having a variety of genetic and environmental factors. There is considerable evidence to support the role of toxins, particularly pesticides and herbicides, in at least some of those affected (presumably, mostly the genetically vulnerable). The pathogenesis of autism is no less complex, but little is known about the potential role of toxins for autism, a neurodevelopmental disorder. The incidence of autism appears to be rising, and early exposure to synthetic chemicals is one suspect for this rise. Impaired detoxification of certain chemicals may be common to autism and Parkinson's disease. Further study of environmental influences for either disorder may lead to important insights regarding causation for both, and perhaps for other neurodegenerative and neurodevelopmental disorders as well. (C) 2001 Harcourt Publishers Ltd.

Worobey BL. 1986 Jan-Feb. Potential neurotoxicity of NaBH4 reduced paraquat. J Anal Toxicol 10(1):40.

Wu J, Chan P, Schroeder KM, Ellsworth K, Partridge LDL. 2002. 1-Methyl-4-phenylpridinium (MPP+)-induced functional run-down of GABA(A) receptor-mediated currents in acutely dissociated dopaminergic neurons . J Neurochem 83(1):87-99.
Abstract: We have evaluated GABA(A) receptor function during treatment of 1-methyl-4-phenylpridinium (MPP+ ) using patch-clamp perforated whole-cell recording techniques in acutely dissociated dopaminergic (DAergic) neurons from rat substantia nigra compacta (SNc). gamma-Aminobutyric acid (GABA), glutamate or glycine induced inward currents (I (GABA) , I (Glu) , I (Gly) ) at a holding potential (V (H) ) of -45 mV. The I (GABA) was reversibly blocked by the GABA(A) receptor antagonist, bicuculline, suggesting that I (GABA) is mediated through the activation of GABA(A) receptors. During extracellular perfusion of MPP+ (1-10 mum), I (GABA) , but neither I (Glu) nor I (Gly) , declined (termed run-down) with repetitive agonist applications, indicating that the MPP+ -induced I (GABA) run-down occurred earlier than I (Gly) or I (Glu) under our experimental conditions. The MPP+ -induced I (GABA) run-down can be prevented by a DA transporter inhibitor, mazindol, and can be mimicked by a metabolic inhibitor, rotenone. Using conventional whole-cell recording with different concentrations of ATP in the pipette solution, I (GABA) run-down can be induced by decreasing intracellular ATP concentrations, or prevented by supplying intracellular ATP, indicating that I (GABA) run-down is dependent on intracellular ATP concentrations. A GABA(A) receptor positive modulator, pentobarbital (PB), potentiated the declined I (GABA) and eliminated I (GABA) run-down. Corresponding to these patch-clamp data, tyrosine hydroxylase (TH) immunohistochemical staining showed that TH-positive cell loss was protected by PB during MPP+ perfusion. It is concluded that extracellular perfusion of MPP+ induces a functional run-down of GABA(A) receptors, which may cause an imbalance of excitation and inhibition of DAergic neurons.

Wu XF, Block ML, Zhang W, Qin L, Wilson B, Zhang WQ, Veronesi B, Hong JS.

2005. The role of microglia in paraquat-induced dopaminergic neurotoxicity. Antioxidants & Redox Signaling 7(5-6):654-661.
Abstract: The herbicide paraquat (PQ) has been implicated as a potential risk factor for the development of Parkinson's disease. In this study, PQ (0.5-1 mu M) was shown to be selectively toxic to dopaminergic (DA) neurons through the activation of microglial NADPH oxidase and the generation of superoxide. Neuron-glia cultures exposed to PQ exhibited a decrease in DA uptake and a decline in the number of tyrosine hydroxylase-immunoreactive cells. The selectivity of PQ for DA neurons was confirmed when PQ failed to alter gamma-aminobutyric acid uptake in neuron-glia cultures. Microglia-depleted cultures exposed to I mu M PQ failed to demonstrate a reduction in DA uptake, identifying microglia as the critical cell type mediating PQ neurotoxicity. Neuron-glia cultures treated with PQ failed to generate tumor necrosis factor-alpha and nitric oxide. However, microglia-enriched cultures exposed to PQ produced extracellular superoxide, supporting the notion that microglia are a source of PQ-derived oxidative stress. Neuron-glia cultures from NADPH oxidase-deficient (PHOX-/-) mice, which lack the functional catalytic subunit of NADPH oxidase and are unable to produce the respiratory burst, failed to show neurotoxicity in response to PQ, in contrast to PHOX+/+ mice. Here we report a novel mechanism of PQ-induced oxidative stress, where at lower doses, the indirect insult generated from microglial NADPH oxidase is the essential factor mediating DA neurotoxicity.

Wu YR. 2005 Jun. Pesticides and Parkinson's disease. Acta Neurol Taiwan 14(2): 38-9.

Xu GP, Perez-Pinzon MA, Sick TJ. 2003. Mitochondrial Complex I inhibition produces selective damage to hippocampal subfield CA1 in organotypic slice cultures. Neurotoxicity Research 5(7):529-537.
Abstract: The effects of mitochondrial respiratory chain inhibitors and the excitotoxin N-methyl-D-aspartate (NMDA) on cell death in hippocampal subfields CA1 and CA3 were examined in hippocampal organotypic slice cultures. Slice cultures, 2-3 week old, were exposed for 1 h to either the Complex I inhibitors, rotenone or 1-methyl-4-phenylpyridium (MPP+), the Complex II inhibitor 3-nitropropionic acid (3-NP), or the excitotoxin NMDA. Cell death was examined 24 and 48 h following treatment, by measuring propidium iodide (PI) fluorescence. Treatment with 1 muM rotenone caused greater cell death in hippocampal subfield CA1 than CA3. Exposure of hippocampal slice cultures to 10 muM rotenone, to MPP+ or to NMDA resulted in damage to both CA1 and CA3 subfields. 3-NP produced little damage in either subfield. The data suggest that mitochondrial complex I inhibition can produce selective cell damage in hippocampus and in this regard is similar to that observed following hypoxia/ischemia.

Yamin G, Munishkina LA, Karymov MA, Lyubchenko YL, Uversky VN, Fink AL. 2005. Forcing nonamyloidogenic beta-synuclein to fibrillate. Biochemistry (Mosc) 44(25):9096-9107.
Abstract: The fibrillation and aggregation of alpha-synuclein is a key process in the formation of intracellular inclusions, Lewy bodies, in

substantia nigral neurons and, potentially, in the pathology of Parkinson's disease and several other neurodegenerative disorders. alpha-Synuclein and its homologue P-synuclein are both natively unfolded proteins that colocalize in presynaptic terminals of neurons in many regions of the brain, including those of dopamine-producing cells of the substantia nigra. Unlike its homologue, P-synuclein does not form fibrils and has been shown to inhibit the fibrillation of alpha-synuclein. In this study, we demonstrate that fast and efficient aggregation and fibrillation of beta-synuclein can be induced in the presence of a variety of factors. Certain metals (Zn2+, Pb2 +, and Cu2+) induce a partially folded conformation of beta-synuclein that triggers rapid fibrillation. In the presence of these metals, mixtures of alpha- and beta-synucleins exhibited rapid fibrillation. The metal-induced fibrillation of beta-synuclein was further accelerated by the addition of glycosaminoglycans or high concentrations of macromolecular crowding agents. beta-Synuclein also rapidly formed soluble oligomers and fibrils in the presence of pesticides, whereas the addition of low concentrations of organic solvents induced formation of amorphous aggregates. These new findings demonstrate the potential effect of environmental pollutants in generating an amyloidogenic, and potentially neurotoxic, conformation, in an otherwise benign protein.

Yang J, Hu LF, Liu X, Zhou F, Ding JH, Hu G. 2005 Oct 7. Effects of iptakalim on extracellular glutamate and dopamine levels in the striatum of unilateral 6-hydroxydopamine-lesioned rats: A microdialysis study. Life Sci . Abstract: In a previous study, we demonstrated that iptakalim (Ipt) significantly ameliorated hypolocomotion and catalepsy induced by haloperidol and rotenone in rats. In order to further understand the mechanism(s), using a rat model of Parkinson's disease (PD) established by unilateral 6-hydroxydopamine (6-OHDA) administration to the substantia nigra pars compacta (SNpc) and reverse microdialysis techniques with high performance liquid chromatography (HPLC), we investigated the effects of Ipt on extracellular levels of glutamate, dopamine (DA) and its metabolite dihydroxyphenylacetic acid (DOPAC) in the striatum of conscious and freely moving rats. The results indicated that unilateral 6-OHDA-lesioned rats have a significantly higher level of extracellular glutamate and a lower level of extracellular DOPAC in the lesioned-side of the striatum, and a lower level of extracellular DA in both sides of the striatum compared to the striatum of control rats. Ipt reduced extracellular glutamate levels in both sides of striatum of the lesioned and control rats in a concentration-dependent manner. Ipt, at lower concentrations (0.01, 0.1, 1 muM), enhanced extracellular DA levels in the lesioned-side striatum of the unilateral 6-OHDA-lesioned rats, while causing no significant changes in the intact side striatum, and even a significant decline in striatum of control rats at higher concentrations of Ipt (10, 100 muM). In addition, Ipt also caused a significant decline in the extracellular DOPAC levels in the lesioned-side striatum of unilateral 6-OHDA-lesioned rats. These data suggest that the major mechanism underlying the ameliorative effects of Ipt on the behavior in 6-OHDA-lesioned rats is the alteration of levels of extracellular neurotransmitters, such as glutamate

and DA in the striatum of unilateral 6-OHDA-lesioned rats.

Yang MC, Mclean AJ, Le Couteur DG. 2002. Age-related alteration in hepatic disposition of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and pesticides. Pharmacology & Toxicology 90(4):203-207.
Abstract: Idiopathic Parkinson's disease may be caused by environmental neurotoxins such as pesticides, however the major risk factor is old age. We postulated that the high incidence of Parkinson's disease in older people is secondary to age-related impairment of the hepatic detoxification of xenobiotics. Previously, we have shown that there are significant differences between the hepatic disposition of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and pesticides. Here, we investigated whether there are age-related differences in the hepatic disposition of MPTP and pesticides, putatively associated with the pathogenesis of Parkinson's disease, We measured the hepatic disposition of paraquat, dichlorodiphenyltrichloroethane (DDT), malathion and MPTP using the multiple indicator dilution technique in the perfused livers of Fischer F344 rats aged 3 and 18 months. The recoveries of MPTF DDT and malathion were increased from the livers of the older rats (by 258%, 253% and 134% compared with young rats, respectively). The hepatic transport of DDT and malathion into hepatocytes was reduced with age suggesting that part of the impaired uptake of neurotoxins may be secondary to an age-related barrier to influx. Ageing may increase risk of Parkinson's disease by altering hepatic detoxification and increasing systemic bioavailability of neurotoxins.

Yang MC, Mclean AJ, Rivory LP, Le Couteur DG . 2000. Hepatic disposition of neurotoxins and pesticides. Pharmacology & Toxicology 87(6):286-291.
Abstract: The hepatic disposition of pesticides and neurotoxins may influence susceptibility to Parkinson's disease. Therefore we examined the behaviour of paraquat, dichlorodiphenyltrichloroethane (DDT), malathion and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in perfused rat liver using the multiple indicator-dilution technique. The values for the recovery of paraquat, DDT, malathion and MPTP were 1.05+/-0.12, 0.32 +/-0.01, 0.11+/-0.02. and 0.02+/-0.01, respectively. The volumes of distribution were 0.28+/-0.13, 0.69+/-0.12, 3.30+/-0.58 and 5.10+/-6.00 ml/g, respectively The permeability-surface area products suggest that transport of DDT and MPTP across cell membranes is by simple diffusion. However, there may be a specific influx mechanism for malathion and a specific efflux mechanism for paraquat. There is considerable variability in the hepatic disposition of putative neurotoxins such as MPTP and pesticides. Factors that influence the hepatic disposition of neurotoxins may alter susceptibility to neurotoxic diseases however the effects will be diverse.

Yang WL, Sun AY. 1998. Paraquat-induced cell death in PC12 cells. Neurochem Res 23(11):1387-1394.
Abstract: Paraquat was taken up by PC12 cells in a carrier-mediated, saturable manner. When PC12 cells were permeabilized with digitonin (50 mu g/ml) lipid peroxidation was observed after paraquat treatment in the

presence of NADPH and chelated iron. The fact that lipid peroxidation preceded the appearance of LDH release provides positive evidence that lipid peroxidation may be one of the important factors leading to cytotoxicity of cells. Furthermore, the fact that addition of superoxide dismutase, catalase and promethazine efficiently blocked the malondialdehyde formation and attenuated the cell death indicated the involvement of reactive oxygen radicals in mediating the cytotoxicity induced by paraquat. Taken together the results present in vitro evidence that neurotoxicity of paraquat may be a consequence of cellular lipid peroxidation, which leads to cell death and may have great implications in assessing the risk of exposure to paraquat in Parkinson's disease.

Yang WL, Sun AY. 1998. Paraquat-induced free radical reaction in mouse brain microsomes. Neurochem Res 23(1):47-53.
Abstract: Paraquat has been implicated as an environmental toxin which may induce the syndrome of Parkinson's disease after exposure to this agent. However, the biochemical mechanism by which paraquat causes cell death and neurodegeneration has not been extensively studied. Paraquat was rapidly taken up by nerve terminals isolated from mouse cerebral cortices. It induced lipid peroxidation in a concentration dependent manner in the presence of NADPH and ferrous ion. The maximal stimulation effect was obtained at a paraquat concentration around 100 mu M and the K-m value for paraquat was 46.7 mu M. The lipid peroxidation required microsomal enzymes. Antioxidants, such as superoxide dismutase, catalase and promethazine significantly inhibited paraquat-induced lipid peroxidation. Due to its structural similarity to the pyridinium compound MPP+ (N-methyl-4-phenyl pyridium ion), it may be taken up by dopamine neurons and cause lipid peroxidation and cell death resulting in the manifestation of Parkinsonian syndrome.

Yang WS, Tiffany-Castiglioni E. 2005. The bipyridyl herbicide paraquat produces oxidative stress-mediated toxicity in human neuroblastoma SH-SY5Y cells: Relevance to the dopaminergic pathogenesis. Journal of Toxicology and Environmental Health-Part a-Current Issues 68(22):1939-1961.
Abstract: Paraquat (PQ) is a cationic nonselective bipyridyl herbicide widely used to control weeds and grasses in agriculture. Epidemiologic studies indicate that exposure to pesticides can be a risk factor in the incidence of Parkinson's disease (PD). A strong correlation has been reported between exposure to paraquat and PO incidence in Canada, Taiwan, and the United States. This correlation is supported by animal studies showing that paraquat produces toxicity in dopaminergic neurons of the rat and mouse brain. However, it is unclear how paraquat triggers toxicity in dopaminergic neurons. Based on the prooxidant properties of paraquat, it was hypothesized that paraquat may induce oxidative stress-mediated toxicity in dopaminergic neurons. To explore this possibility, dopaminergic SH-SY5Y cells were treated with paraquat, and several biomarkers of oxidativestress were measured. First, a specific dopamine transporter inhibitor GBR12909 significantly protected SY5Y cells against the toxicity of paraquat, indicating that paraquat exerts its toxicity by a mechanism involving the dopamine transporter (DAT). Second, paraquat increased

intracellular levels of reactive oxygen species (ROS), but decreased the levels of glutathione. Third, paraquat inhibited glutathione peroxidase activity, but did not affect glutathione reductase activity. On the other hand, paraquat increased GST activity by 24 h, after which GST activity returned to the control value at 48 h. Fourth, paraquat dissipated mitochondrial transmembrane potential (MTP). Fifth, paraquat produced increases of malondialdehyde (MDA) and protein carbonyls, as well as DNA fragmentation, indicating oxidative damage to major cellular components. Sixth, paraquat increased the protein level of heme oxygenase-1 (HO-1). Taken together, these findings verify our hypothesis that paraquat produces oxidative stress-mediated toxicity in SH-SY5Y cells. Thus, current findings suggest that paraquat may induce the pathogenesis of dopaminergic neurons through oxidative stress.

Yang Y, Liu X, Ding JH, Sun J, Long Y, Wang F, Yao HH, Hu G. 2004. Effects of iptakalim on rotenone-induced cytotoxicity and dopamine release from PC12 cells. Neurosci Lett 366(1):53-57.
Abstract: Parkinson's disease is characterized by an extensive loss of dopaminergic neurons in the substantia nigra pars compacta. The final common pathway in the demise of these cells may involve dopamine-dependent oxidative stress. Previous studies revealed a new neuronal protective role of ATP-sensitive potassium channel openers. But the exact mechanism is still unknown. In the present study, the neuroprotective effect of iptakalim, a novel ATP-sensitive potassium channel opener, was studied against rotenone-induced cytotoxicity in rat dopaminergic PC12 cells. Rotenone decreased cell viability significantly after 48 h exposure and induced dopamine release from PC12 cells concentration-dependently. Iptakalim significantly enhanced dopamine uptake and alleviated rotenone-induced PC12 cells death and reduced dopamine release induced by rotenone or GBR-12909, a classical dopamine transporter inhibitor. These results suggest that iptakalim may open mitochondrial K-ATP channels to modulate dopamine transporter and reduce extracellular dopamine levels, thereby it protecting PC12 cells against rotenone-induced injury. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Yang Y, Liu X, Long Y, Wang F, Ding JH, Liu SY, Sun YH, Yao HH, Wang H, Wu J, Hu G. 2005. Systematic administration of iptakalim, an ATP-sensitive potassium channel opener, prevents rotenone-induced motor and neurochemical alterations in rats. J Neurosci Res 80(3):440-447.
Abstract: Our previous studies revealed that iptakalim, a novel ATP-sensitive potassium channel opener, has a significant neuroprotective function against ischemia in vivo or rotenone-induced neurotoxicity in vitro. To investigate the potential pharmaceutical benefit of ATP-sensitive potassium channel openers on neurodegenerative diseases, we studied the effects of iptakalim and diazoxide, a selective mitochondrial ATP-sensitive potassium channel opener, on the rotenone-induced nigrostriatal degeneration in rats. lptakalim (1.5 mg/kg/day, orally) or diazoxide (1.5 mg/kg/day, orally) alone was administered to rats for 3 days, and then for 4 weeks was used daily with an injection of rotenone (2.5 mg/kg/day, subcutaneously) 1 hr later each time. The results showed that rotenone-

infused rats exhibited parkinsonian symptoms and had dopamine depletion in the striatum and substantia nigra. Pretreatment with iptakalim or diazoxide prevented rotenone-induced catalepsy and the reduction of striatum dopamine contents. Moreover, iptakalim and diazoxide reduced the enzymatic activities and mRNA levels of inducible nitric oxide synthase elicited by chronic administration of rotenone. These neuroprotective effects of iptakalim and diazoxide were abolished by 5-hydroxydecanoate, a selective mitochondrial ATP-sensitive potassium channel blocker. In conclusion, our data suggested that mitochondrial ATP-sensitive potassium channels might play a key role in preventing both parkinsonian symptoms and neurochemistry alterations induced by rotenone in rats. The selective activation of mitochondrial ATP-sensitive potassium channels may provide a new therapeutic strategy for prevention and treatment of neurodegenerative disorders such as Parkinson's disease. (c) 2005 Wiley-Liss, Inc.

Yang Y, Liu X, Long Y, Wang F, Ding JH, Liu SY, Sun YH, Yao HH, Wang H, Wu J, Hu G. 2005 May 1. Systematic administration of iptakalim, an ATP-sensitive potassium channel opener, prevents rotenone-induced motor and neurochemical alterations in rats. J Neurosci Res 80(3):442-9.
Abstract: Our previous studies revealed that iptakalim, a novel ATP-sensitive potassium channel opener, has a significant neuroprotective function against ischemia in vivo or rotenone-induced neurotoxicity in vitro. To investigate the potential pharmaceutical benefit of ATP-sensitive potassium channel openers on neurodegenerative diseases, we studied the effects of iptakalim and diazoxide, a selective mitochondrial ATP-sensitive potassium channel opener, on the rotenone-induced nigrostriatal degeneration in rats. Iptakalim (1.5 mg/kg/day, orally) or diazoxide (1.5 mg/kg/day, orally) alone was administered to rats for 3 days, and then for 4 weeks was used daily with an injection of rotenone (2.5 mg/kg/day, subcutaneously) 1 hr later each time. The results showed that rotenone-infused rats exhibited parkinsonian symptoms and had dopamine depletion in the striatum and substantia nigra. Pretreatment with iptakalim or diazoxide prevented rotenone-induced catalepsy and the reduction of striatum dopamine contents. Moreover, iptakalim and diazoxide reduced the enzymatic activities and mRNA levels of inducible nitric oxide synthase elicited by chronic administration of rotenone. These neuroprotective effects of iptakalim and diazoxide were abolished by 5-hydroxydecanoate, a selective mitochondrial ATP-sensitive potassium channel blocker. In conclusion, our data suggested that mitochondrial ATP-sensitive potassium channels might play a key role in preventing both parkinsonian symptoms and neurochemistry alterations induced by rotenone in rats. The selective activation of mitochondrial ATP-sensitive potassium channels may provide a new therapeutic strategy for prevention and treatment of neurodegenerative disorders such as Parkinson's disease.

Yang Y, Liu X, Long Y, Wang F, Ding JH, Liu SY, Sun YH, Yao HH, Wang H, Wu J, Hu G. 2006 Feb. Activation of mitochondrial ATP-sensitive potassium channels improves rotenone-related motor and neurochemical alterations in rats. Int J Neuropsychopharmacol 9(1):51-61.

Abstract: Our previous studies revealed that activation of mitochondrial ATP-sensitive potassium channels exerted protective effects on rotenone-treated rats and cultured cells. The aim of the present study is to examine the potential therapeutic effects of iptakalim, an ATP-sensitive potassium-channel opener, and diazoxide, a selective mitochondrial ATP-sensitive potassium-channel opener, on Parkinsonian symptoms in rats induced by rotenone. Rats were treated with rotenone (2.5 mg/kg s.c.) daily for 4 wk. This treatment caused a depletion of dopamine in the striatum and substantia nigra. Behaviourally, rotenone-infused rats exhibit Parkinsonian symptoms. Catalepsy was estimated by a 9-cm bar test. Treatment with L-dopa (10 mg/kg.d p.o.), iptakalim (0.75, 1.5, 3.0 mg/kg.d p.o.) and diazoxide (3.0 mg/kg.d p.o.) for 2 wk improved behavioural dysfunction and elevated dopamine contents in the striatum and substantia nigra of rotenone-treated rats. Studies also found that iptakalim and diazoxide could reduce the enzymic activities and mRNA levels of inducible nitric oxide synthase elicited by chronic administration of rotenone. All neurorestorative effects by both iptakalim and diazoxide were abolished by 5-hydroxydecanoate, a selective mitochondrial ATP-sensitive potassium-channel blocker. Collectively, the data suggested that mitochondrial ATP-sensitive potassium channels play a key role in improving both Parkinsonian symptoms and neurochemistry alterations of rotenone model rats, and selective activation of mitochondrial ATP-sensitive potassium channels may provide a new therapeutic strategy for treatment of early Parkinson's disease.

Yang YL, Meng CH, Ding JH, He HR, Ellsworth K, Wu J, Hu G. 2005. Iptakalim hydrochloride protects cells against neurotoxin-induced glutamate transporter dysfunction in in vitro and in vivo models. Brain Res 1049(1): 80-88.

Abstract: Iptakalim hydrochloride (Ipt), a novel antihypertensive drug, exhibits K-ATP channel activation. Here, we report that Ipt remarkably protects cells against neurotoxin- induced glutamate transporter dysfunction in in vitro and in vivo models. Chronic exposure of cultured PC12 cells to neurotoxins, such as 6-OHDA, MPP+, or rotenone, decreased overall [H-3]-glutamate uptake in a concentration-dependent manner. Pre-treatment using 10 M Ipt significantly protected cells against neurotoxin-induced glutamate uptake diminishment, and this protection was abolished by the K-ATP channel blocker glibenclamide (20 mu M), suggesting that the protective mechanisms may involve the opening of K-ATP channels. In 6-OHDA-treated rats (as an in vivo Parkinson's disease model), [H-3]-glutamate uptake was significantly lower in synaptosomes isolated from the striatum and cerebral cortex, but not the hippocampus. Pre-conditioning using 10, 50, and 100 mu M Ipt significantly restored glutamate uptake impairment and these protections were abolished by blockade of K-ATP channels. It is concluded that Ipt exhibits substantial protection of cells against neurotoxicity in in vitro and in vivo models. The cellular mechanisms of this protective effect may involve the opening of K-ATP channels. Collectively, Ipt may serve as a novel and effective drug for PD therapy. 

Yesavage JA, Sheikh J, Noda A, Murphy G, O'hara R, Hierholzer R, Battista M, Ashford JW, Kraemer HC, Tinklenberg J. 2004. Use of a VA pharmacy database to screen for areas at high risk for disease: Parkinson's disease and exposure to pesticides. J Geriatr Psychiatry Neurol 17(1):36-38.
Abstract: The purpose of this study was to assess whether pharmacy database information from US Department of Veterans Affairs (VA) medical centers could be used to screen for areas of higher Parkinson's disease prevalence in patients exposed to pesticides. The authors used pharmacy data sets and compared the use of antiparkinsonian medications at 2 VA medical centers in California: one in Palo Alto, near the ocean, and one in Fresno, downwind from extensively farmed parts of the Central Valley. They found that patients at Fresno had higher odds ratios (1.5-1.8) for the use of Parkinson's disease medications than patients at Palo Alto. These data are consistent with the observations of prior epidemiologic studies and suggest that VA pharmacy databases can prioritize locations for further epidemiologic research. However, a thorough exploration of alternative explanations is needed to reach definitive conclusions regarding the findings suggested by this method.

Yogev-Falach M, Amit T, Bar-Am O, Weinstock M, Youdim MBH. 2002. The involvement of mitogen-activated protein (MAP) kinase in the regulation of amyloid precursor protein processing by novel cholinesterase inhibitors derived from rasagiline. FASEB J 16(10 ).
Abstract: Two novel neuroprotective cholinesterase (ChE) inhibitors, TV3326, (N-propargyl-(3R) aminoindan-5-yl)-ethyl methyl carbamate, and TV3279, (N-propargyl-(3S) aminoindan-5-yl)ethyl methyl carbamate, were derived from rasagiline for the treatment of Alzheimer's disease (AD). TV3326 also inhibits monoamine oxidase (MAO)-A and -B, whereas its S-isomer, TV3279, lacks MAO inhibitory activity. The action of these drugs in the regulation of amyloid precursor protein (APP) processing, using rat PC12 and human SH-SY5Y neuroblastoma cells, was examined. Both isomers stimulated the release of the non-amyloidogenic alpha-secretase form of soluble APP (sAPP) from these cell lines. The increases in sAPP induced by TV3326 and TV3279, were dose-dependent (0.1-100 muM) and blocked by the hydroxamic acid-based metalloprotease inhibitor, Ro31-9790, suggesting mediation via alpha-secretase activity. Using several signal transduction inhibitors, we identified the involvement of protein kinase C (PKC), mitogen-activated protein (MAP) kinase, and tyrosine kinase-dependent pathways in the enhancement of sAPP release by TV3326 and TV3279. In addition, both drugs directly induced the phosphorylation of p44 and p42 MAP kinase, which was abolished by the specific inhibitors of MAP kinase activation, PD98059 and U0126. These data suggest a novel pharmacological mechanism whereby these ChE inhibitors regulate the secretory processes of APP via activation of the MAP kinase pathway.

Yoshikawa T, Minamiyama Y, Naito Y, Kondo M. 1994. Antioxidant properties of bromocriptine, a dopamine agonist. J Neurochem 62(3):1034-1038.
Abstract: It has been suggested that free radicals may adversely influence the pathogenesis of Parkinson's disease. We conducted this study to

determine whether bromocriptine, an agent widely used for treating parkinsonism, possesses antioxidant effects. Bromocriptine scavenged superoxide produced from a superoxide generating system (hypoxanthine-xanthine oxidase) by the spin-trapping method using electron spin resonance. Bromocriptine had a strong scavenging effect an the 5,5-dimethyl-1-pyrroline-N-oxide hydroxide signal produced from Fenton's reaction. Bromocriptine also attenuated the stable free radical diphenyl-p-picrylhydrazyl signal. This drug inhibited the autooxidation of rat brain homogenates in a dose-dependent manner in vitro. Autooxidation of brain homogenates collected from rats treated with bromocriptine (2.5 mg/kg, i.p., daily for 3 days) was significantly reduced as compared with Values in untreated rat homogenates. These observations suggest that bromocriptine is a free radical scavenger and a potent antioxidant.

Youdim MB, Amit T, Bar-Am O, Weinstock M, Yogev-Falach M. 2003 May. Amyloid processing and signal transduction properties of antiparkinson-antialzheimer neuroprotective drugs rasagiline and TV3326. Ann N Y Acad Sci 993:378-86; discussion 387-93.
Abstract: Two novel neuroprotective cholinesterase (ChE) inhibitors, TV3326 and TV3279 [(N-propargyl-(3R) and (3S) aminoindan-5-yl)-ethyl methyl carbamate], respectively were derived from rasagiline, for the treatment of Alzheimer's disease (AD). TV3326 also inhibits monoamine oxidase (MAO)-A and B, while its S-isomer, TV3279, lacks MAO-inhibitory activity. The actions of these drugs in the regulation of the amyloid precursor protein (APP) processing using rat PC12 and human SH-SY5Y neuroblastoma cells were examined. Both isomers stimulated the release of the non-amyloidogenic alpha-secretase form of soluble APP (sAPPalpha) from these cell lines. The increases in sAPPalpha, induced by TV3326 and TV3279, were dose-dependent (0.1-100 micro M) and blocked by the hydroxamic acid-based metalloprotease inhibitor, Ro31-9790, suggesting mediation via alpha-secretase activity. Using several signal transduction inhibitors, the involvement of protein kinase C (PKC), mitogen-activated protein (MAP) kinase, and tyrosine kinase-dependent pathways in the enhancement of sAPPalpha release by TV3326 and TV3279 was identified. In addition, both drugs directly induced the phosphorylation of p44 and p42 MAP kinase, which was abolished by the specific inhibitors of MAP kinase activation, PD98059 and U0126. These data suggest a novel pharmacological mechanism, whereby these ChE inhibitors regulate the secretary processes of APP via activation of the MAP kinase pathway.

Youdim MB, Weinstock M. 2004 Jan. Therapeutic applications of selective and non-selective inhibitors of monoamine oxidase A and B that do not cause significant tyramine potentiation. Neurotoxicology 25(1-2):243-50 .
Abstract: The major side effect with the use of first generation of non selective monoamine oxidase (MAO) inhibitors as neuropsychiatric drugs was what became known as the "cheese reaction". Namely, potentiation of sympathomimetic activity of ingested tyramine present in cheese and other food stuff, resulting from its ability to release noradrenaline, when prevented from metabolism by MAO. The identification of two forms of MAO, termed types A and B and their selective irreversible inhibitors

resolved some of this problems. However irreversible MAO-A inhibitors continue to induce a cheese reaction, whereas MAO-B inhibitors at their selective dosage did not and led to introduction of L-deprenyl (selegiline) as an anti-Parkinson drug, since dopamine is equally well metabolized by both enzyme forms. The cheese reaction is a consequence of inhibition of MAO-A, the enzyme responsible for metabolism of noradrenaline and serotonin, located in peripheral adrenergic neurons. The consequence of these findings were the development of reversible MAO-A inhibitors (RIMA), moclobemide and brofaromin, as antidepressants and possible anti-Parkinson activity, with limited tyramine potentiation, since the amine can displace the inhibitor from its binding site on the enzyme. It has always been deemed a greater pharmacological advantage to inhibit both forms of the enzymes to get the full functional activities of the amine neurotransmitters, and without inducing a "cheese reaction". This was not possible until recently, with the development of the novel cholinesterase-brain selective MAO-AB inhibitor, TV3326 (N-propargyl-(3R)-aminoidnan-5-yl-ethyl methylcarbamate hemitartiate), a carbamate derivative of the irreversible MAO-B inhibitor anti-Parkinson drug, rasagiline. This drug is a brain selective MAO-A and B inhibitor, with little inhibition of liver and small intestine enzymes. Pharmacologically it has limited tyramine potentiation, very similar to moclobemide and being a MAO-AB inhibitor it has the antidepressant, anti-Parkinson and anti-Alzheimer activities in the respective models used to develop such drugs.

Youdim MBH, Finberg JPM. 1994. Pharmacological actions of l-deprenyl (selegiline) and other selective monoamine-oxidase-b inhibitor. Clinical Pharmacology & Therapeutics 56(6):725-733.
Abstract: The acetylenic selective monoamine oxidase (MAO) type B suicide inhibitor, l-deprenyl (l-selegiline), has proved to be a useful adjuvant to L-dopa therapy and monotherapy of Parkinson's disease. Although not all features of its antiParkinson action are known, studies that used brains obtained at autopsy from patients who took l-deprenyl show that the selective inhibition of MAO-B with a concomitant increase of phenylethylamine and dopamine, but not of serotonin or noradrenaline, in the basal ganglia may be responsible for its mode of action. The increased Life expectancy noted in patients with Parkinson's disease who received long-term therapy (9 years in an uncontrolled study) is another unexpected feature of the drug. These exciting data, if confirmed in other long-term clinical trials, may herald a neuroprotective approach to the treatment of this degenerative disease. More recent studies indicate that Parkinson's disease may eventually turn out to be a neurotoxic event resulting from oxidative stress-induced free radical species in the substantia nigra. Thus selective MAO-B inhibitors could represent a unique class of drugs, having symptomatic actions with possible neuroprotective and neurorescue actions in one.

Youdim MBH, Fridkin M, Zheng HL. 2005. Bifunctional drug derivatives of MAO-B inhibitor rasagiline and iron chelator VK-28 as a more effective approach to treatment of brain ageing and ageing neurodegenerative diseases. Mech Ageing Dev 126(2):317-326.

Abstract: Degeneration of nigrostriatal dopamine neurons and cholinergic cortical neurones are the main pathological features of Parkinson's disease (PD) and for the cognitive deficit in dementia of the Alzheimer' type (AD) and in dementia with Lewy bodies (DLB), respectively. Many PD and DLB subjects have dementia and depression resulting from possible degeneration of cholinergic and noradrenergic and serotonergic neurons. On the other hand, AD patients may also develop extrapyramidal features as well as depression. In both PD and AD there is, respectively, accumulation of iron within the melanin containing dopamine neurons of pars compacta and with in the plaques and tangle. It has been suggested that iron accumulation may contribute to the oxidative stress induced apoptosis reported in both diseases. This may result from increased glia hydrogen peroxide producing monoamine oxidase (MAO) activity that can generate of reactive hydroxyl radical formed from interaction of iron and hydrogen peroxide. We have therefore prepared a series of novel bifunctional drugs from the neuroprotective-antiapoptotic antiparkinson monoamine oxidase B inhibitor, rasagiline, by introducing a carbamate cholinesterase (ChE) inhibitory moiety into it. Ladostigil (TV-3326, N-propargyl-3R-aminoindan-5yl)-ethyI methylcarbamate), has both ChE and MAO-AB inhibitory activity, as potential treatment of AD and DLB or PD subjects with dementia Being a brain selective MAO-AB inhibitor it has limited potentiation of the pressor response to oral tyramine and exhibits antidepressant activity similar to classical non-selective MAO inhibitor antidepressants by increasing brain serotonin and noradrenaline. Ladostigil inhibits brain acetyl and butyrylcholinesterase in rats and antagonizes scopolamine-induced inhibition of spatial learning. Ladostigil like MAO-B inhibitor it prevents MPTP Parkinsonism in mice model and retains the in vitro and in vivo neuroprotective activity of rasagiline. Ladostigil, rasagiline and other propargylamines have been demonstrated to have neuroprotective activity in several in vitro and in vivo models, which have been shown be associated with propargylamines moiety, since propargylamines itself possess these properties. The mechanism of neuroprotective activity has been attributed to the ability of propargylarnines-inducing the antiapoptotic family proteins Bcl-2 and Bcl-xl, while decreasing Bad and Bax and preventing opening of mitochondrial permeability transition pore. Iron accumulates in brain regions associated with neurodegenerative diseases of PD, AD, amyotrophic lateral sclerosis and Huntington disease. It is thought to be involved in Fenton chemistry oxidative stress observed in these diseases. The neuroprotective activity of propargylamines led us to develop several novel bifunctional iron chelator from our prototype brain permeable iron chelators, VK-28, possessing propargylamine moiety (HLA-20, M30 and M30A) to iron out iron from the brain. These compounds have been shown to have iron chelating and monoamine oxidase A and B selective brain inhibitory and neuroprotective-antiapoptotic actions. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

Youdim MBH, Weinstock M. 2001. Molecular basis of neuroprotective activities of rasagiline and the anti-Alzheimer drug TV3326 [(N-propargyl-3R) aminoindan-5-YL)-ethyl methyl carbamate. Cell Mol Neurobiol 21(6):

555-573.
Abstract: Rasagiline (N-propargyl-1-(R)-aminoindan) is a selective, irreversible monoamine oxidase B (MAO B) inhibitor which has been developed as an anti-Parkinson drug. In controlled monothetapy and as adjunct to L-dopa it has shown anti-Parkinson activity. In cell culture (PC-12 and neuroblastoma SH-SY5Y cells) it exhibits neuroprotective and antiapoptotic activity against several neurotoxins (SIN-1, MPTP, 6-hydroxydopamine and N-methyl-(R)-salsolinol) and ischemia. In vivo, it reduces the sequelae of traumatic brain injury in mice and speeds their recovery. The neuroprotective activity of rasagaline does not result from MAO B inhibition, since its S-enantiomer, TVP1022, which has 1000-fold weaker MAO inhibitory activity, exhibits similar neuroprotective properties. Introduction of a carbamate moiety into the rasagiline molecule to confer cholinesterase inhibitory activity for the treatment of Alzheimer's disease, resulted in compounds TV3326 [(N-Propargyl-(3R)Aminoindan-5-YL)-Ethyl Methyl Carbamate] and its S-enantiomer TV3279 [(N-Proparagyl-(3S) Aminoindan-5-YL)-Ethyl Methyl Carbamate], which retain the neuroprotcetive activities of rasagiline and TYP1022. They also antagonize scopolamine-induced impairments in spatial memory. In addition, TV3326 exhibits brain-selective MAO A and B inhibitory activity after chronic administration and has antidepressant-like activity in the forced swim test. This is associated with an increase in brain levels of serotonin. The antiapoptotic activity of these propargylamine-containing derivatives may be related to their ability to delay the opening of voltage-dependent anion channels (VDAC), which are part of the mitochondrial permeability transition pore, The propargylamine moiety is responsible for the increase in the mitochondrial family of Bcl-2 proteins, prevention in the fall in mitochondrial membrane potential, prevention of the activation of caspase 3, and of translocation of glycerlaldehyde-3-phosphate dehydrogenase from the cytoplasm to the nucleus. The latter processes are closely associated with neurotoxin-induced apoptosis. Rasagiline interacts with and prevents the binding of PK11195 to the pro-apoptotic peripheral benzodiazepine receptor, which together with Bcl-2, hexokinase, porin, and adenine nucleotide translocator constitutes part of the VDAC. Furthermore, rasagiline, TV3326 and TV3279 are able to influence the processing of amyloid precursor protein by activation of alpha-secretase and increasing the release of soluble alpha APP in rat PC-12 and human neuroblastoma SH-SY5Y cells and in rat and mice cortex and hippocampus. This process has been shown to involve the upregulation of PKC and MAP kinase. It is quite likely that the induction of Bcl-2 and activation of PKC by rasagiline and TV3326 is closely linked to the anti-apototic action of these drugs and their ability to process APP by activation of alpha-secretase.

Youdim MBH, Weinstock M. 2002. Novel neuroprotective anti-Alzheimer drugs with anti-depressant activity derived from the anti-Parkinson drug, rasagiline. Mech Ageing Dev 123(8):1081-1086.
Abstract: A number of studies have shown that the selective monoamine oxidase (MAO)-B inhibitor l-selegiline has neuroprotective activities in several cell culture systems and in vivo. The suggestion has been made

that the propargyl moiety in this molecule may have some intrinsic neuroprotective activity not related to its ability to bind covalently to MAO B and inhibit it. We have therefore developed a number of novel drugs based on rasagiline (N-propargyl-1 R-(+)-aminoindan), a potent anti-Parkinson-propargyl-containing MAO-B inhibitor drug with structural resemblance to selegiline, for the treatment of Alzheimer's disease. These drugs possess a carbamate moiety for cholinesterase (ChE), and a propargyl group for MAO inhibition. The R-enantiomer of these compounds (TV3326) has ChE and MAO inhibitory activities in vivo and retains the neuroprotective properties of rasagiline. It also exhibits antidepressant activity in animal models. The S-enantiomer does not inhibit MAO and has no anti-depressant activity, but it has similar ChE inhibitory and neuroprotective activities. Thus MAO inhibition by propargylamines is not a pre-requisite for neuroprotection. Rather, propargylamines have some intrinsic neuroprotective property whose mechanism of action requires further elucidation. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Yumino K, Kawakami I, Tamura M, Hayashi T, Nakamura M. 2002. Paraquat- and diquat-induced oxygen radical generation and lipid peroxidation in rat brain microsomes. J Biochem (Tokyo) 131(4):565-570.
Abstract: NADPH-menadione reductase activity by rat brain microsomes (Ms) was decreased 40-50% by 10 muM dicumarol, a potent inhibitor of DT-diaphorase, whereas no change in NADPH-paraquat (PQ) and -diquat (DQ) reductase activity was observed. NADPH-DQ reductase activity in brain Ms was 2.5-fold higher than NADPH-PQ reductase activity. The formation of PQ and DQ radicals was verified optically and observed directly by ESR spectroscopy in the NADPH-PQ and -DQ reductase reactions by brain Ms under anaerobic conditions. PQ- and DQ-induced superoxide formation was confirmed by the detection of DMPO-OOH ESR signals and followed by chemiluminescence (CL) of a Cypridina luciferin analogue (CIA). The kinetics and intensity of the CL were consistent with the observations that the reduction in DQ is faster than that in PQ. Thiobarbituric acid reactive substances (TBARS) and phospholipid hydroperoxides in brain Ms increased in the presence of NADPH and Fe3+. The generation of both lipid peroxidation products derived from brain Ms decreased with increasing concentrations of PQ and DQ. The inhibitory effect of DQ is more pronounced than that of PQ. The formation of PQ- and DQ-induced reactive oxygen species was not associated with lipid peroxidation in rat brain Ms.

Zayed J, Ducic S, Campanella G, Panisset JC, Andre P, Masson H, Roy M. 1990 Aug. [Environmental factors in the etiology of Parkinson's disease]. Can J Neurol Sci 17(3):286-91.
Abstract: We examined the role of the environment in the development of Parkinson's disease (PD). A group of 42 parkinsonians have been compared with a group of 84 matched controls. The epidemiological study (1987-1989) covered the territory of the Community Health Department of Valleyfield, in southern Quebec (Canada). Odds ratio adjusted for age and sex were calculated for seven environmental factors. A decreased risk for

PD was associated with residence in rural areas (OR: 0.31; p less than or equal to 0.05) and residence near industry or mining (OR: 0.15; p less than or equal to 0.05). An increased risk for PD seems to be associated with occupational exposure to the three metals Mn, Fe and Al (OR: 2.28; p = 0.07) especially when the duration of exposure is longer than 30 years (OR: 13.64; p less than or equal to 0.05). Other environmental factors not found to be associated with PD were: pesticides manipulation, farm work, industrial work and well water consumption.

Zecca L, Tampellini D, Gerlach M, Riederer P, Fariello RG, Sulzer D. 2001. Substantia nigra neuromelanin: structure, synthesis, and molecular behaviour. Journal of Clinical Pathology-Molecular Pathology 54(6): 414-418.
Abstract: The pigmented neurones of the substantia nigra are typically lost in Parkinson's disease; however, the possible relation between neuronal vulnerability and the presence of neuromelanin has not been elucidated. Early histological studies revealed the presence of increasing amounts of neuromelanin in the substantia nigra with aging in higher mammals, showed that the neuromelanin granules are surrounded by a membrane, and comparatively evaluated the pigmentation of the substantia nigra in different animal species. Histochemical studies showed the association of neuromelanin with lipofuscins. However, systematic investigations of the structure, synthesis, and molecular interactions of neuromelanin have been undertaken only during the past decade. In these later studies, neuromelanin was identified as a genuine melanin with a strong chelating ability for iron and an affinity for compounds such as lipids, pesticides, and MPP+. The affinity of neuromelanin for a variety of inorganic and organic toxins is consistent with a postulated protective function for neuromelanin. Moreover, the neuronal accumulation of neuromelanin during aging and the link between its synthesis and a high cytosolic concentration of catechols suggest a protective role. However, its putative neuroprotective effects could be quenched in conditions of toxin overload.

Zecca L, Zucca FA, Costi P, Tampellini D, Gatti A, Gerlach M, Riederer P, Fariello RG, Ito S, Gallorini M, Sulzer D. 2003. The neuromelanin of human substantia nigra: structure, synthesis and molecular behaviour. Journal of Neural Transmission-Supplement (65):145-155.
Abstract: The pigmented neurons of the substantia nigra (SN) are typically lost in Parkinson's disease: however the possible relationship between neuronal vulnerability and the presence of neuromelanin (NM) has not been elucidated. Early histological studies revealed the presence of increasing amounts of NM in the SN with aging in higher mammals, showed that NM granules are surrounded by membrane, and comparatively evaluated the pigmentation of SN in different animal species. Histochemical studies showed the association of NM with lipofuscins. However, systematic investigations of NM structure, synthesis and molecular interactions have been undertaken only during the last decade. In these latter studies, NM was identified as a genuine melanin with a strong chelating ability for iron and affinity for compounds such as lipids, pesticides, and MPP+. The affinity of NM for a variety of inorganic and organic toxins is consistent with

a postulated protective function for NM. Moreover, the neuronal accumulation of NM during aging, and the link between its synthesis and high cytosolic concentration of catechols suggests a protective role. However, its putative neuroprotective effects could be quenched in conditions of toxin overload.

Zecca L, Zucca FA, Wilms H, Sulzer D. 2003. Neuromelanin of the substantia nigra: a neuronal black hole with protective and toxic characteristics. Trends Neurosci 26(11):578-580.
Abstract: Neuromelanin accumulates in dopaminergic neurons during normal aging, and in Parkinson's disease, neurons with this pigment are those that selectively degenerate. Intraneuronal neuromelanin could play a protective role during its synthesis by preventing the toxic accumulation of cytosolic catechol derivatives and, in addition, by its ability to scavenge reactive metals, pesticides and other toxins to form stable adducts. However, dying neurons in Parkinson's disease that release neuromelanin might induce a vicious cycle of chronic neuroinflammation and neuronal loss.

Zeevalk GD, Bernard LP. 2005. Energy status, ubiquitin proteasomal function, and oxidative stress during chronic and acute complex I inhibition with rotenone in mesencephalic cultures. Antioxidants & Redox Signaling 7 (5-6):662-672.
Abstract: Complex I impairment with rotenone produces damage though a mechanism thought to be distinct from effects on mitochondrial respiration. The outcome of chronic rotenone on energy status in relation to toxicity, however, is unknown. To examine this, mesencephalic cultures were exposed to chronic, low-dose rotenone (5-100 nM, 8 days in vitro) or acute, high-dose rotenone (500 nM, 1-24 h), and ATP/ADP levels and toxicity were measured. Chronic exposure to 5-50 nM rotenone produced selective dopamine cell loss. High-dose rotenone produced nonselective damage at all exposure times. Chronic, low-dose rotenone (37.5 nM) decreased ATP/ADP gradually over several days to 40% of controls, whereas high-dose rotenone (500 nM, 1-6 h), collapsed ATP/ADP by I h of exposure. The ubiquitin proteasomal pathway, an ATP-dependent pathway, is implicated in Parkinson's disease and, thus, various rotenone exposures were examined for effects on ubiquitin proteasomal function. Chronic, low-dose rotenone (25-50 nM, 8 days), but not acute, high-dose rotenone (500 nM, 1-6 h), caused accumulation of ubiquitinated proteins, El-ubiquitin activation, and increased proteasomal activities prior to toxicity even though both exposures increased free radical production. Findings show that selective dopamine cell loss and alterations in ubiquitin proteasomal function only occur with rotenone exposures that partially maintain ATP/ ADP. High concentrations of rotenone that collapse energy status kill neurons in a nonselective manner independent of the ubiquitin proteasomal pathway.

Zejda JE, Mcduffie HH, Dosman JA. 1993. Epidemiology of health and safety risks in agriculture and related industries - practical applications for rural physicians. West J Med 158(1):56-63.

Abstract: Epidemiologic studies document that work in the agricultural sector is associated with many occupational health hazards. Exposure to organic dusts and airborne microorganisms and their toxins may lead to respiratory disorders. The burden of exposure-related chronic bronchitis, asthma, hypersensitivity pneumonitis, organic-dust toxic syndrome, and chronic airflow limitation can be diminished by appropriate preventive measures. The contribution of exposures to agricultural chemicals to cancers and neurodegenerative disorders is being investigated. Some studies document that farmers and those in related industries are at higher risk for the development of cancer of the stomach, soft tissue sarcoma, non-Hodgkin's lymphoma, and multiple myeloma. Chronic encephalopathy and Parkinson's and Alzheimer's diseases are being studied in relation to agricultural chemicals. The possible carcinogenicity and neurotoxicity of pesticides emphasize the need to promote the safe use of chemicals. Another area for health promotion programs is disabling injuries and traumatic deaths. Farm accidents are important because of their frequent occurrence among young people and disturbing fatality rates. Other health issues of concern in these industries include skin diseases, hearing loss, and stress.

Zhang J, Fitsanakis VA, Gu GY, Jing DQ, Ao MF, Amarnath V, Montine TJ. 2003. Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. J Neurochem 84(2):336-346.
Abstract: Manganese ethylene-bis-dithiocarbamate (Mn-EBDC) is the major active element of manab, a pesticide linked to parkinsonism in certain individuals upon chronic exposure. Additionally, it has been shown to produce dopaminergic neurodegeneration in mice systemically coexposed to another pesticide, 1,1'-dimathyl-4,4'-bipyridinium (paraquat). Here, we described a rat model in which selective dopaminergic neurodegeneration was produced by delivering Mn-EBDC directly to the lateral ventricles. After establishing this model, we tested whether Mn-EBDC provoked dopamine efflux in the striatum, a well-known phenomenon produced by the mitochondrial inhibitor 1-methyl-4-phenylpyridinium (MPP), the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that causes parkinsonism in humans, as well as in some animals. Finally, we investigated whether Mn-EBDG directly inhibited mitochondrial function in vitro using isolated brain mitochondria. Our data demonstrated that Mn-EBDG induced extensive striatal dopamine efflux that was comparable with that induced by MPP+, and that Mn-EBDC preferentially inhibited mitochondrial complex Ill. As mitochondrial dysfunction is pivotal in the pathogenesis of Parkinsons disease (PD), our results support the proposal that exposure to pesticides such as maneb, or other naturally occurring compounds that inhibit mitochondrial function, may contribute to PD development.

Zheng S, Chou AH, Jimenez AL, Khodadadi O, Son S, Melega WP, Howard BD. 2002. The fetal and neonatal brain protein neuronatin protects PC12 cells against certain types of toxic insult. Developmental Brain Research 136(2): 101-110.

Abstract: The protein neuronatin is expressed in the nervous system of the fetus and neonate at a much higher level than in the adult. Its function is unknown. As a result of variable splicing, neuronatin mRNA exists in two forms, alpha and beta. Wild type PC 12 cells express neuronatin-alpha. We have isolated a PC12 variant, called 1.9, that retains many of the neuron-like properties of wild type PC12 cells, but it does not express neuronatin and it exhibits markedly increased sensitivity to the toxic effects of nigericin, rotenone and valinomycin. Pretreatment of the 1.9 cells with alpha-methyltyrosine, which inhibits dopamine synthesis, had little effect on the cells' sensitivity to nigericin, rotenone or valinomycin indicating that dopamine-induced oxidative stress was not involved in the toxicity of these compounds. However, flattened cell subvariants of the 1.9 cells, which do not have any neuron-specific characteristics, did not exhibit increased sensitivity to nigericin indicating that some neuronal characteristic of the 1.9 cells contributed to the toxicity of nigericin. After the neuronatin-beta gene was transfected into and expressed in the 1.9 cells, they regained wild type PC12 levels of resistance to nigericin, rotenone and valinomycin. These studies suggest that the function of neuronatin during development could be to protect developing cells from toxic insult occurring during that period. (C) 2002 Elsevier Science B.V.

Zhou Y, Gu GY, Goodlett DR, Zhang T, Pan C, Montine TJ, Montine KS, Aebersold RH, Zhang J. 2004. Analysis of alpha-synuclein-associated proteins by quantitative proteomics. J Biol Chem 279(37):39155-39164.
Abstract: To identify the proteins associated with soluble alpha-synuclein (AS) that might promote AS aggregation, a key event leading to neurodegeneration, we quantitatively compared protein profiles of AS-associated protein complexes in MES cells exposed to rotenone, a pesticide that produces parkinsonism in animals and induces Lewy body (LB)-like inclusions in the remaining dopaminergic neurons, and to vehicle. We identified more than 250 proteins associated with Nonidet P-40 soluble AS, and demonstrated that at least 51 of these proteins displayed significant differences in their relative abundance in AS complexes under conditions where rotenone was cytotoxic and induced formation of cytoplasmic inclusions immunoreactive to anti-AS. Overexpressing one of these proteins, heat shock protein (hsp) 70, not only protected cells from rotenonemediated cytotoxicity but also decreased soluble AS aggregation. Furthermore, the protection afforded by hsp70 transfection appeared to be related to suppression of rotenone-induced oxidative stress as well as mitochondrial and proteasomal dysfunction.

Zhou Y, Shie FS, Piccardo P, Montine TJ, Zhang J. 2004. Proteasomal inhibition induced by manganese ethylene-bis-dithiocarbamate: Relevance to Parkinson's disease. Neuroscience 128(2):281-291.
Abstract: Maneb, a widely used fungicide, has been associated with Parkinsonism in humans. In experimental models, maneb and its major active element, manganese ethylenebis-dithiocarbamate (Mn-EBDC) cause selective nigrostriatal neurodegeneration in mice and in rats, respectively. To investigate the mechanisms underlying this neurodegeneration, we studied the effects of Mn-EBDC on proteasomal function, which is

decreased in patients with Parkinson's disease (PD), in a dopaminergic neuronal cell line (MES 23.5 or MES). The results demonstrated that exposure of MES cells to 6 muM Mn-EBDC for 7 days produced not only significant neurotoxicity but also inhibition of proteasomal chymotrypsin-like and postglutamyl peptidase activities. Proteasomal dysfunction was accompanied by formation of cytoplasmic inclusions that were positive for a-synuclein immunostaining and significantly increased sodium dodecyl sulfate-insoluble alpha-synuclein aggregation seen by Western blot analysis. In addition, there was a significant increase in oxidative stress, evidenced by elevated total protein carbonyl content, in cells treated with Mn-EBDC. Manipulation of intracellular reduced glutathione levels with N-acetyl-L-cysteine or L-buthionine sulfoximine pretreatment to modulate Mn-EBDC-mediated oxidative stress altered Mn-EBDC-mediated neurotoxicity, proteasomal dysfunction, and alpha-synuclein aggregation in these cells. These data suggest that neurotoxicityinduced by Mn-EBDC is at least partially attributable to Mn-EBDC-mediated proteasomal inhibition, and that the proteasome may be an important target by which environmental exposure modifies the risk for developing PD in vulnerable populations. (C) 2004 IBRO. Published by Elsevier Ltd. All rights reserved.

Zhou Y, Wang Y, Kovacs M, Jin JH, Zhang J. 2005. Microglial activation induced by neurodegeneration - A proteomic analysis. Molecular & Cellular Proteomics 4(10):1471-1479.
Abstract: Neuroinflammation mediated by microglial activation appears to play an essential role in the pathogenesis of Parkinson disease; however, the mechanisms by which microglia are activated are not fully understood. Thus, we first evaluated the effects of two parkinsonian toxicants, manganese ethylene bisdithiocarbamate (Mn-EBDC) and 1-methyl-4-phenylpyridine (MPP+), on microglial activation as well as associated dopaminergic (DAergic) neurotoxicity in primary cell culture systems. The results demonstrated that, when rat primary mesencephalic neuron-enriched or neuron-microglia mixed cultures were treated with Mn-EBDC at 2 - 8 mu M or MPP+ at 0.25 - 5 mu M, respectively, for 7 days, both toxicants were capable of inducing DAergic neurodegeneration as well as activating microglia via a mechanism secondary to DAergic neurodegeneration. Furthermore activated microglia subsequently enhanced DAergic neurotoxicity induced by Mn- EBDC or MPP+. Detailed scrutiny of neuron-microglia interactions identified a fraction of the conditioned media derived from a DAergic cell line treated with Mn- EBDC or MPP+ that potently activated microglia. To further define potential mediators leading to microglial activation secondary to neurodegeneration, we utilized a quantitative proteomic technique termed SILAC ( for stable isotope labeling by amino acids in cell culture) to compare the protein profiles of MPP+-treated cellular fraction that mediated microglial activation as compared with controls. The search revealed numerous novel proteins that are potentially important in neurodegeneration-mediated microglial activation, a process believed to be critical in Parkinson disease progression.

Zhu CN, Vourc'h P, Fernagut PO, Fleming SM, Lacan S, Dicarlo CD, Seaman RL,

Chesselet MF. 2004. Variable effects of chronic subcutaneous administration of rotenone on striatal histology. J Comp Neurol 478 (4): 418-426.
Abstract: When infused in rats, rotenone, a mitochondrial complex I inhibitor, induces alterations that resemble the histological changes of Parkinson's disease, particularly degeneration of the nigrostriatal dopaminergic system. However, the specificity of rotenone effects has been challenged recently. We have re-examined the alterations caused by rotenone in the substantia nigra and the striatum of rats after infusion of rotenone (2 mg/kg per day s.c.) for 21 days. Three patterns of striatal tyrosine-hydroxylase immunoreactivity (TH-IR) were observed: 46% of animals showed no reduction, and 46% of animals showed diffuse reduction in TH-IR, whereas one animal presented a focal loss of TH-IR in the striatum. Confocal microscopy analysis showed that the vesicular monoamine transporter (VMAT2) was decreased in parallel with TH-IR, strongly suggesting a loss of striatal DA nerve terminals in animals with diffuse or central TH-IR loss. However, no significant loss of TH-IR neurons was observed in the substantia nigra. Analysis of NeuN and DARPP-32 immunoreactivity, and Nissl staining, in the striatum showed no striatal neuronal loss in animals with either preserved TH-IR or diffuse TH-IR reduction. However, in the animal with focal TH-IR loss, severe neuronal loss was evident in the center and the periphery of the striatum, together with microglial activation detected by OX-6 and OX-42 staining. Thus, in most cases, chronic subcutaneous infusion of low doses of rotenone does not induce significant striatal neuronal loss, despite TH-IR and VMAT-IR reduction in a subset of animals, supporting the use of rotenone as a model of Parkinson's disease under carefully controlled experimental conditions. (C) 2004 Wiley-Liss, Inc.

Zhuo M, Yu FR, Xu DH, Sun LY, Liu XY. 2003. Baculovirus p35 gene greatly enhances PC12 cell's resistance against oxidative stress. J Neurol Sci 216 (1):135-141.
Abstract: Oxidative stress is thought to be a major contributor to the progress of the Parkinson's Disease (PD) because of the high vulnerability of dopaminergic cells against oxidative stress. The present work demonstrates that with the expression of the baculovirus p35 gene, PC12 cells could gain a high resistance against oxidative toxicants, hydrogen peroxide (H2O2) and 6-hydroxydopamine (6-OHDA). The DNA fragmentation analysis showed that PC12 cells underwent apoptosis after exposure to H2O2 or 6-OHDA, while PP35 cells, a p35-expressing PC12 cell line, did not. Flow cytometric analysis showed that treatment with 150 muM H2O2 or 120 muM 6-OHDA for 24 h caused 52.86% or 66.36% apoptotic cell, respectively, in PC12 cells, but only 4.26% or 5.80% in PP35 cells. The cell viability measured by 3-(4,5-dimethylthiazal-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay indicated that H2O2 and 6-OHDA induced a dose-dependent cell death on PC12 cells that were greatly remitted on PP35 cells. The viability of PP35 cells was even stronger than that of PC12 cells protected by glial cell line deprived neurotrophic factor (GDNF). The surviving PP35 cells remained normal cell morphology and showed positive

with tyrosine hydroxylase (TH) immunocytochemical staining. These results indicate that baculovirus p35 gene possesses remarkable ability to rescue PC12 cells from death in experimental paradigms associated with oxidative stress. (C) 2003 Elsevier B.V. All rights reserved.

Zielinska E, Kocki T, Saran T, Borbely S, Kuc D, Vilagi I, Urbanska EM, Turski WA. 2005. Effect of pesticides on kynurenic acid production in rat brain slices. Ann Agric Environ Med 12(2):177-179.
Abstract: Kynurenic acid (KYNA) is a broad spectrum antagonist of ionotropic glutamate receptors, preferentially active at the strychnine-insensitive glycine allosteric site of the N-methyl-D-aspartate (NMDA) receptor, and a noncompetitive antagonist of alpha7 nicotinic receptor. Animal studies showed that it possesses anticonvulsant and neuroprotective properties. Its involvement in the pathophysiology of various brain disorders was suggested. In this study, the effect of pesticides on KYNA production in brain cortical slices was investigated. Pyrethroids, deltaniethrin and fenpropathrin significantly lowered KYNA production. Methomyl, bensultap, fipronil, diquat and MCPA were ineffective in this regard. In view of this data, the inhibition of KYNA synthesis appear to merit further investigation as a potential factor contributing to the toxicology of pyrethroids.

Zilker T, Fogt F, Vonclarmann M. 1988. No parkinsonism after acute paraquat poisoning. Klin Wochenschr 66(22):1138-1141.

Ziv I, Barzilai A, Offen D, Nardi N, Melamed E. 1997. Nigrostriatal neuronal death in Parkinson's disease - a passive or an active genetically-controlled process? Journal of Neural Transmission-Supplement (49):69-76.
Abstract: The cause for the rather selective degeneration of the nigrostriatal dopaminergic (DA) neurons in Parkinson's disease (PD) is still enigmatic. The major current hypothesis suggests that nigral neuronal death in PD is due to excessive oxidant stress generated by auto- and enzymatic oxidation of DA, formation of neuromelanin and presence of high concentrations of iron. Such cell death is generally regarded as a passive, necrotic process, mainly resulting from membrane lipid peroxidation, leading to its dysfunction and rupture and then to neuronal disintegration. We suggest a novel approach, that views neuronal degeneration in PD as an active process that occurs mainly the nuclear level. Our concept is based on the following observations: (1) Nigral histopathology in PD is characterized by a slow, protracted degeneration of individual neurons. We propose that it may be due to apoptosis [programmed cell-death (PCD), an active, genetically-controlled, intrinsic program of cell ''suicide''] rather than to necrotic cell death. (2) DA exerts antitumor effect on melanoma and neuroblastoma cells. (3) Many anticancer drugs, trigger PCD by causing DNA damage. (4) DA has been shown to be genotoxic. (5) We recently first showed that DA, the endogenous neurotransmitter in the nigra, can trigger apoptosis in cultured, postmitotic sympathetic neurons. (6) We have also shown that PC-12 cells, transfected with the bcl-2 gene (a proto-oncogene that inhibits PCD) are relatively resistant to DA-apoptotic effect. Degeneration of

nigrostriatal neurons in PD may therefore be linked to dysregulation of the control mechanisms that normally restrain the PCD-triggering-potential of their own neurotransmitter.

Ziv I, Zilkhafalb R, Offen D, Shirvan A, Barzilai A, Melamed E. 1997. Levodopa induces apoptosis in cultured neuronal cells - A possible accelerator of nigrostriatal degeneration in Parkinson's disease? Mov Disord 12(1):17-23.
Abstract: Apoptosis is an active, intrinsic cell suicide program. We recently suggested that it may have a role in the death of nigrostriatal dopaminergic neurons in Parkinson's disease (PD). We now report that levodopa, the current major therapy for PD, is a potent inducer of apoptosis in cultured postmitotic chick sympathetic neurons. Levodopa, in a concentration range of 0.01-0.3 mM, caused the characteristic apoptotic cascade of cell shrinkage, massive membrane blebbing, and nuclear fragmentation, as evident by nuclear flow cytometry and fluorescence microscopy. Levodopa-induced apoptosis was inhibited by antioxidants, indicating that it may be mediated by autooxidation-reactive species. Levodopa treatment for PD may therefore constitute an additional challenge for the defective apoptosis-inhibiting systems in the nigrostriatal neurons. Despite reassuring data from some, but not all, previous studies, these findings suggest that the possible in vivo toxic effects of levodopa on the survival of the remaining nigral neurons should be further explored.

Zoccarato F, Cavallini L, Alexandre A. 2004. Respiration-dependent removal of exogenous H2O2 in brain mitochondria - Inhibition by Ca2+. J Biol Chem 279(6):4166-4174.
Abstract: In brain mitochondria, state 4 respiration supported by the NAD-linked substrates glutamate/malate in the presence of EGTA promotes a high rate of exogenous H2O2 removal. Omitting EGTA decreases the H2O2 removal rate by almost 80%. The decrease depends on the influx of contaminating Ca2+, being prevented by the Ca2+ uniporter inhibitor ruthenium red. Arsenite is also an inhibitor (maximal effect similar to40%, IC50, 12 muM). The H2O2 removal rate (EGTA present) is decreased by 20% during state 3 respiration and by 60-70% in fully uncoupled conditions. H2O2 removal in mitochondria is largely dependent on glutathione peroxidase and glutathione reductase. Both enzyme activities, as studied in disrupted mitochondria, are inhibited by Ca2+. Glutathione reductase is decreased by 70% with an IC50 of about 0.9 muM, and glutathione peroxidase is decreased by 38% with a similar IC50. The highest Ca2+ effect with glutathione reductase is observed in the presence of low concentrations of H2O2. With succinate as substrate, the removal is 50% less than with glutamate/malate. This appears to depend on succinate-supported production of H2O2 by reverse electron flow at NADH dehydrogenase competing with exogenous H2O2 for removal. Succinate-dependent H2O2 is inhibited by rotenone, decreased DeltaPsi, as described previously, and by ruthenium red and glutamate/malate. These agents also increase the measured rate of exogenous H2O2 removal with succinate. Succinate-dependent H2O2 generation is also inhibited by contaminating Ca2+. Therefore, Ca2+ acts as an inhibitor of both H2O2 removal and the succinate-supported H2O2 production. It is concluded that mitochondria

function as intracellular Ca2+-modulated peroxide sinks.

Zoccarato F, Toscano P, Alexandre A. 2005. Dopamine-derived dopaminochrome promotes H2O2 release at mitochondrial complex I - Stimulation by rotenone, control by Ca2+, and relevance to Parkinson disease. J Biol Chem 280(16):15587-15594.
Abstract: Inhibitors of Complex I of the mitochondrial respiratory chain, such as rotenone, promote Parkinson disease-like symptoms and signs of oxidative stress. Dopamine (DA) oxidation products may be implicated in such a process. We show here that the o-quinone dopaminochrome (DACHR), a relatively stable DA oxidation product, promotes concentration (0.1 - 0.2 mu M)- and respiration-dependent generation of H2O2 at Complex I in brain mitochondria, with further stimulation by low concentrations of rotenone ( 5 - 30 nM). The rotenone effect required that contaminating Ca2+ ( 8 - 10 mu M) was not removed. DACHR apparently extracts an electron from the constitutively autoxidizable site in Complex I, producing a semiquinone, which then transfers an electron to O-2, generating O-2(radical anion) and then H2O2. Mitochondrial removal of H2O2, formed by either monoamine oxidase activity or DACHR, was performed largely by glutathione peroxidase and glutathione reductase, which were negatively regulated by low intramitochondrial Ca2+ levels. Thus, the H2O2 formed accumulated in the medium if contaminating Ca2+ was present; in the absence of Ca2+, H2O2 was completely removed if it originated from monoamine oxidase, but was less completely removed if it originated from DACHR. We propose that the primary action of rotenone is to promote extracellular O-2. release via activation of NADPH oxidase in the microglia. In turn, O-2. oxidizes DA to DACHR extracellularly. ( The reaction is favored by the lack of GSH, which would otherwise preferably produce GSH adducts of dopaminoquinone.) Once formed, DACHR ( which is resistant to GSH) enters neurons to activate the rotenone-stimulated redox cycle described.

Zorzon M, Capus L, Pellegrino A, Cazzato G, Zivadinov R. 2002. Familial and environmental risk factors in Parkinson's disease: a case-control study in north-east Italy. Acta Neurol Scand 105(2):77-82.
Abstract: Background and objective - The aetiology of Parkinson's disease remains unknown, although both genetic susceptibility and environmental factors are considered putative contributors to its origin. We performed a case-control study to investigate the association of familial and environmental risk factors with Parkinson's disease (PD). Methods - We studied 136 patients with neurologist confirmed PD and 272 age- and sex-matched controls, affected by neurological diseases not related to PD. The risk of developing idiopathic PD associated with the following familial and environmental factors: positive family history of PD, positive family history of essential tremor (ET), age of mother at subject's birth. rural birth, rural living, well water use, farming as an occupation, exposure to pesticides, head tremor, exposure to general anaesthesia and to ionizing radiations, food restriction, concentration camp imprisonment and smoking has been assessed by using univariate and multivariate statistical techniques. Results - In the conditional multiple logistic regression analysis, positive

family history of PD (OR 41.7, 95% CI 12.2-142.5, P < 0.0001), positive family history of ET (OR 10.8, 95% CI 2.6-43.7, P < 0.0001), age of mother at subject's birth (OR 2.6. 95% CI 1.4-3.7, P = 0.0013), exposure to general anaesthesia (OR 2.2, 95% CI 1.3-3.8, P = 0.0024), farming as an occupation (OR 7.7, 95% CI 1.4-44.1, P = 0.0212) and well water use (OR 2.0, 95% CI 1.1-3.6 P = 0.0308) exhibited a significant positive association with PD, whereas smoking showed a trend toward an inverse relationship with PD (OR 0.7, 95% CI 0.4-1.1, P < 0.06). Conclusions - We conclude that both familial and environmental factors may contribute to PD aetiology.

Zubenko GS. 1990. Significance of increased platelet membrane fluidity in mental disorders of late-life. Ups J Med Sci Suppl 48:225-44.
Abstract: Increased platelet membrane fluidity, as determined by the fluorescence anisotropy of 1,6-diphenyl-1,3,5-hexatriene (DPH), appears to be a stable, inherited trait that identifies a prominent subgroup of patients with Alzheimer's disease with distinct clinical features. Evidence bearing on the clinical and biological significance of this genetic source of clinical heterogeneity in Alzheimer's disease is presented.

Zuber M, Alperovitch A. 1991. Parkinsons-disease and environmental-factors. Rev Epidemiol Sante Publique 39(4):373-387.
Abstract: The etiology of the nigrostriatal pathway degeneration in Parkinson's disease (PD) is unknown but there is a growing pool of evidence that environmental factors may be involved in the genesis of this disorder. The discovery of the N-Methyl 4-Phenyl 1, 2, 3, 6-Tetrahydro-Pyridine (MPTP)-induced injury in late 1970s provided the first experimental model of PD and stimulated dramatically the epidemiological research. An excitotoxic amino acid contained in cycad, which is thought to be responsible for the amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam, provides another exemple of toxin-induced parkinsonism. This amino acid is present in most seeds common in the Western diet. In developed countries, prevalence of PD is 2 to 5 times as high than in developing countries. PD patients in developed countries are more likely than controls to have lived in rural environment. Case control studies have suggested that this positive association is possibly related to pesticides and herbicides exposures or well water drinking. Dietary surveys are now going on and several hypothesis are tested including high MPTP-structural analogs or seeds consumption in PD patients and low antioxydants consumption. The negative association between smoking habits and PD has been recognized for more than 20 years. There is evidence that this association is not an artefact due to the disease affecting smoking habits. Its origin is unknown but it could provide important aetiological clues for PD. The most recent hypothesis concerning the relationships between these environmental factors and PD are reviewed and pertinent suitable surveys for the future are discussed.

Zucca FA, Giaveri G, Gallorini M, Albertini A, Toscani M, Pezzoli G, Lucius R, Wilms H, Sulzer D, Ito S, Wakamatsu K, Zecca L. 2004. The neuromelanin of human substantia nigra: Physiological and pathogenic aspects. Pigment

Cell Res 17(6):610-617.
Abstract: Neuromelanin (NM) accumulates as a function of age in normal human substantia nigra (SN) but is relatively depleted in the SN of patients with Parkinson disease (PD). Several studies have been performed to further our understanding of the role of NM in neuronal aging and neurodegenerative mechanisms of PD. To this purpose, NM from human SN was isolated and its structure and molecular interactions were investigated. Cysteinyl-dopamine was shown to be one precursor of NM synthesis. A striking affinity of NM for specific metals, lipids, drugs and pesticides was found in vitro, and in animal and human brain postmortem studies. Because of these affinities, NM seems to play a protective role in the human brain by blocking toxic molecules. On the other hand, experiments in cell culture indicate that NM can activate microglia, eliciting the release of cytotoxic factors that can induce neurodegeneration.

Zuddas A, Fascetti F, Corsini GU, Piccardi MP. 1994. In brown-norway rats, mpp (+) is accumulated in the nigrostriatal dopaminergic terminals but it is not neurotoxic - a model of natural-resistance to mptp toxicity. Exp Neurol 127 (1):54-61.
Abstract: Rats have been described as being insensitive to relatively high doses of systemically administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that in primates induces a neurological syndrome identical to idiopathic Parkinson's disease. The current explanation for the rat resistance is that most of the MPTP is converted into the toxic metabolite 1-methyl-4-phenylpyridium (MPP(+)) by the MAO-B present in the brain vessel endothelium. Since MPP(+) is a polar compound, a very low amount could cross the blood-brain barrier and be present inside the brain. We administered C57 BL mice and Brown Norway rats with either MPTP (30 mg/kg, ip) or the combined treatment MPTP + diethyldithiocarbamate (DDC). In mice, DDC prolonged the striatal exposure to MPP(+), potentiated the MPTP-induced acute syndrome, and enhanced the MPTP-induced striatal dopamine depletion. In rats, DDC potentiated the MPTP-induced acute syndrome, but no changes in the striatal dopamine were observed after either MPTP or DDC + MPTP administration. Also in rats, however, high doses of MPP+ were measured in the striatum of MPTP-alone treated rats and DDC delayed the MPP(+) elimination from the striatum. When MPTP alone or DDC + MPTP was administered to rats unilaterally lesioned with B-hydroxy dopamine (6-OH-DA), the levels of MPP(+) measured in the intact striatum were significantly higher than those found in the B-OH-DA-lesioned striatum. Taken together these data indicate that in Brown Norway rats MPP(+) could be formed inside the brain and selectively accumulated in the striatal dopaminergic terminals without exerting its neurotoxicity; they also suggest that not only the MPP(+) formation or elimination but also the intraneuronal distribution of MPP(+) could be crucial for species differences in the sensitivity to the toxin. (C) 1994 Academic Press, Inc.

Zuddas A, Vaglini F, Fornai F, Corsini GU. 1992. Selective lesion of the nigrostriatal dopaminergic pathway by mptp and acetaldehyde or diethyldithiocarbamate. Neurochem Int 20:S287-S293.

Abstract: We have previously reported that diethyldithiocarbamate and acetaldehyde enhance MPTP toxicity in mice (Corsini et al. 1986). Here we show that these drugs enhance the depletion of dopamine in the striatum and markedly increase MPTP-induced death of DA neurons in the substantia nigra. This enhancement of MPTP toxicity is specific for the nigro-striatal DA pathway and no recovery occurs, at least for four months after the treatment. Rats, although they show an MPTP-induced acute syndrome similar to the that induced in mice by the combined treatments, appear to be insensitive to both MPTP alone or to combined treatment with diethyldithiocarbamate or acetaldehyde. The selectivity of the permanent bilateral lesions of the nigrostiatal pathway make mice treated with acetaldehyde or diethyldithiocarbamate and MPTP a simple and reliable model for parkinsonism.