Parkinson* & (acetealdehyde, amalgam, benzyl viologen, contaminant*, pollutant*, PCB*, polychlorinated biphenyl*, Aroclor, solvent*, deguelin, cis-methyldioxolane, benzyl viologen)

[Anonymous]. 1984 Jun 22. Street-drug contaminant causing parkinsonism. MMWR Morb Mortal Wkly Rep 33(24):351-2.

[Anonymous]. 1984 Jul 20. Leads from the MMWR. Street-drug contaminant causing parkinsonism. JAMA 252(3):331.

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.

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.

Anderson I. 1985. Heroin contaminant offers clues to parkinsons-disease. New Scientist 105(1441):8.

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.

Andringa G, Cools AR. 2000. The neuroprotective effects of CGP 3466B in the best in vivo model of Parkinson's disease, the bilaterally MPTP-treated rhesus monkey. J Neural Transm Suppl (60):215-25.
Abstract: The propargylamine CGP 3466B prevents dopamine cell death both in vitro and in rodent models of Parkinson's disease. The present study investigates the efficacy of this compound to prevent the behavioral consequences of dopaminergic cell death in the best animal model of Parkinson's disease, the bilaterally MPTP-treated monkey. Rhesus monkeys were bilaterally treated with MPTP, using a two-step procedure: 2.50 mg MPTP was infused into the left carotid artery followed by a second bolus of 1.25 mg into the right carotid artery, 8 weeks later. Subcutaneous injection of either 0.014 mg/kg CGP 3466B (n = 4) or its solvent (distilled water; n = 4), twice daily for fourteen days, started two hours after the second MPTP infusion. A Parkinson rating scale was assessed for the evaluation of the effects. After the first MPTP treatment, the monkeys developed mild to moderate parkinsonian symptoms. The second MPTP treatment strongly increased the severity of Parkinson scores in all control monkeys, as assessed on day 3, 7, 14, 21, 28 and 35 after the second MPTP treatment. In contrast, CGP 3466B nearly completely prevented the increase of parkinsonian symptoms after the second MPTP treatment. The therapeutic effects of CGP 3466B were still present after a washout period of 3 weeks, implying that the effects were not symptomatic. These data are the first to show that the systemic administration of CGP 3466B is able to prevent the development of MPTP-induced motor symptoms in primates. This compound may have great value for inhibiting the progression of the neurodegenerative process in patients with Parkinson's disease.

Andringa G, Eshuis S, Perentes E, Maguire RP, Roth D, Ibrahim M, Leenders KL, Cools AR. 2003. TCH346 prevents motor symptoms and loss of striatal FDOPA uptake in bilaterally MPTP-treated primates. Neurobiol Dis 14(2): 205-217.
Abstract: The neuroprotective efficacy of the propargylamine TCH346 was studied in the primate model of Parkinson's disease, the bilaterally MPTP-treated monkey. Male rhesus monkeys received 2.5 mg MPTP into the left carotid artery and, 8 weeks later, 1.25 mg MPTP into the right carotid artery. Starting 2 h after the second MPTP infusion, either 0.014 mg/kg TCH346 or its solvent was subcutaneously injected twice per day for 14 days. The first MPTP treatment induced mild Parkinson symptoms, reduced right limb movements, and reduced FDOPA uptake in the left striatum. The second MPTP treatment made Parkinson symptoms worse, reduced left limb movements, and reduced FDOPA uptake in the right striatum of solvent-treated monkeys. In contrast, the second MPTP treatment did not further worsen motor symptoms and did not decrease FDOPA uptake in the right striatum of TCH346-treated monkeys. Although the effects of the second MPTP treatment were largely prevented, the effects of the first MPTP treatment were not reversed by TCH346. Immunohistochemical examination confirmed the dramatic loss of dopamine cells in vehicle-treated monkeys and the preservation of these neurons in the right brain side of the TCH346-treated animals. In conclusion, systemic administration

of TCH346 prevented motor symptoms and nigrostriatal degeneration induced by MPTP in primates. (C) 2003 Elsevier Inc. All rights reserved.

Andringa G, Van Oosten RV, Unger W, Hafmans TGM, Veening J, Stoof JC, Cools AR. 2000. Systemic administration of the propargylamine CGP 3466B prevents behavioural and morphological deficits in rats with 6-hydroxydopamine-induced lesions in the substantia nigra. Eur J Neurosci 12(8):3033-3043.
Abstract: The ability of CGP 3466B to attenuate the behavioural and morphological consequences of experimentally induced cell death was investigated in a recently updated animal model of Parkinson's disease. 6-Hydroxydopamine was infused bilaterally into the substantia nigra pars compacta of rats that were pretreated with desimipramine. Treatment with CGP 3466B (0.0014-1.4 mg/kg, injected subcutaneously) or its solvent was begun 2 h after the 6-OHDA injection, and maintained twice daily for 14 days. After a washout period of 14 days, changes in motor behaviour were evaluated, using the open field test (analysis of normal and abnormal stepping, e.g.) and the paw test (analysis of retraction time of limbs). Changes in learning and memory were evaluated with the help of the Morris water maze task. Following immunocytochemical staining of tyrosine hydroxylase, the extent of the lesion was quantified using a computerized system. CGP 3466B prevented all deficits produced by 6-hydroxydopamine (6-OHDA), though at different doses. It prevented: abnormal stepping (0.0014-0.014 mg/kg); increased forelimb and hindlimb retraction time (0.014-0.14 mg/kg and 0.0014-0.14 mg/kg, respectively); delayed learning (1.4 mg/kg); and reduced tyrosine hydroxylase immunoreactivity in the substantia nigra (0.0014-0.014 mg/kg). CGP 3466B (0.0014-0.14 mg/kg) induced no deficits in sham-treated rats. CGP 3466B (1.4 mg/kg), however, did not show any benefit on motor deficits in 6-OHDA-lesioned rats, and induced abnormal movements and decreased the tyrosine hydroxylase immunoreactivity in the substantia nigra pars compacta and the ventral tegmental area of sham-lesioned animals. It is concluded that CGP 3466B prevents all 6-OHDA-induced behavioural and immunocytochemical deficits, though at different doses. CGP 3466B is suggested to be a valuable agent for inhibiting the dopaminergic degeneration in patients with Parkinson's disease.

[Anon]. 2000. Health and safety - Organic solvents increase Parkinson's risk. Chemistry & Industry (18):591.

Arica B, Kas HS, Moghdam A, Akalan N, Hincal AA. 2005. Carbidopa/levodopa-loaded biodegradable microspheres: in vivo evaluation on experimental Parkinsonism in rats. J Controlled Release 102(3):689-697.
Abstract: The purpose of this study was to prepare and characterize injectable carbidopa (CD)/levodopa (LD)-loaded Poly(L-lactides) (L-PLA), Poly(D,L-lactides) (D,L-PLA) and Poly(D,L-lactide-co-glycolide) (PLAGA) microspheres for the intracerebral treatment of Parkinson's disease. The microspheres were prepared by solvent evaporation method. The polymers' (L-PLA, D,L-PLA and PLAGA) concentrations were 10% (w/w) in the organic phase; the emulsifiers [sodium carboxymethylcellulose (NaCMC):sodium oleate (SO) and Polyvinyl alcohol (PVA):SO mixture (4:1 w/v)] concentrations were 0.75% in the aqueous phase. Microspheres were analyzed for morphological characteristics, size distribution, drug loading and in vitro release. The release profile of CD/LD from microspheres was characterized in the range of 12-35% within the first hour of the in vitro release experiment. The efficiency of CD- and LD-encapsulated microspheres to striatal transplantation and the altering of apomorphine-induced rotational behavior in the 6-hydroxydopamine (6-OHDA) unilaterally lesioned rat model were also tested. 6-OHDA/CD-LD-loaded microsphere groups exhibited lower rotation scores than 6-OHDA/Blank microsphere groups as early as 1 week postlesion. These benefits continued throughout the entire experimental period and they were statistically significant during the 1, 2 and 8 weeks ($p<0.05$). CD/LD-loaded microspheres were specifically prepared to apply as an injectable dosage

forms for brain implantation. (C) 2004 Elsevier B.V. All rights reserved.

Arica B, Kas HS, Orman MN, Hincal AA. 2002. Biodegradable bromocryptine mesylate microspheres prepared by a solvent evaporation technique. I: Evaluation of formulation variables on microspheres characteristics for brain delivery. J Microencapsul 19(4):473-484.
Abstract: The aim of this study was to formulate biodegradable microspheres containing an anti-parkinsonian agent, bromocryptine mesylate, for brain delivery. The effect of formulation parameters (e. g. polymer, emulsifying agent type and concentration) on the characteristics of the microspheres produced, the efficiency of drug encapsulation, the particle size distribution and in vitro drug release rates from the bromocryptine mesylate microspheres were investigated using a 3(2) factorial design. Bromocryptine mesylate was encapsulated into biodegradable polymers using the following three different polymers; poly (L-lactide), poly(D,L-lactide) and poly(D,L-lactide-co-glycolide). The SEM photomicrographs showed that the morphology of the microspheres greatly depended on the polymer and emulsifying agent. The results indicate that, regardless of the polymer type, increase in emulsifying agent concentration from 0.25-0.75% w/v markedly decreases the particle size of the microspheres. Determination of particle size revealed that the use of 0.75% w/v of emulsifying agent concentration and a polymer solution concentration of 10% w/v resulted in optimum particle size. In order to prepare biodegradable microspheres with high drug content and small particle size, selection of polymer concentration as well as emulsifying agent concentration is critical. Polymer type has a less pronounced effect on the percentage encapsulation efficiency and particle size of microspheres than on the t(50%). The microspheres prepared by all three polymers, at a polymer concentration of 10% w/v and an emulsifying agent concentration of 0.75% w/v with NaCMC:SO (4:1, w/v) mixture was as the optimum formulation.

Aschner M, Seegal RF. 2001 Dec. Selected presentations and general discussion: session IX summary and research needs. Neurotoxicology 22(6):849-52.
Abstract: [Parkinson Disease & PCBs, rotenone, thiocarbamates]

Baraldi PG, Cacciari B, Spalluto G, Bergonzoni M, Dionisotti S, Ongini E, Varani K, Borea PA. 1998. Design, synthesis, and biological evaluation of a second generation of pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines as potent and selective A(2A) adenosine receptor antagonists. J Med Chem 41(12): 2126-2133.
Abstract: New A(2A) adenosine receptor antagonists in the series of pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidines, bearing oxygenated substituents on the phenylalkyl chains on the 7-position, have been synthesized. The compounds were tested in binding and functional assays to evaluate affinity, potency, and selectivity for rat A(2A) compared to rat A(1) and human A(3) receptor subtypes. The most interesting compounds (5d,e,h) were tested also in binding to human A(1) and A(2A) adenosine receptors. They showed very good affinity (K-i = 0.94 nM for compound 5h) and interesting selectivity with respect to both rA(1) and hA(3) (compound 5h: rA(1)/rA(2A) = 787, hA(3)/rA(2A) > 10000) These important findings make this new series of compounds the first really selective for A(2A) adenosine receptors. Thermodynamic parameters were evaluated; all the tested compounds displayed an enthalpy-driven binding as expected for antagonists. Moreover, compound 5h showed a negative entropy value. The highly negative enthalpic and entropic contributions could mean that 5h fits very well in the binding site where, probably, an electrostatic interaction is present associated to a scarce solvent reorganization around the receptor binding site. These compounds deserve to be further developed to assess their potential for treatment of neurodegenerative disorders such as Parkinson's disease.

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 PI) 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.

Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T. 2004. Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol 33 (4):894-902.
Abstract: Background Whether dental amalgam fillings (containing mercury) are hazardous is a long-standing issue, with few epidemiological investigations. Allegations have particularly involved nervous system disorders, such as multiple sclerosis, Alzheimer's disease, and chronic fatigue syndrome. This retrospective cohort study, the largest of its kind, contained people in the New Zealand Defence Force (NZDF) between 1977 and 1997. The NZDF has its own dental service, providing all personnel with regular and consistent treatment. Comprehensive treatment records are maintained and archived. Methods Yearly dental treatment histories, including amalgam filling placements, were compiled from individual records. To minimize amalgam exposure misclassification the cohort was restricted to people who, at NZDF entry, were aged <26 years and had all their posterior teeth. The cohort was linked with morbidity records. Data were analysed with a proportional hazards model, using a time-varying exposure unit of 100 amalgam surface-years. Results The final cohort contained 20 000 people, 84% males. Associations with medical diagnostic categories, particularly disorders of the nervous system and kidney, were examined. Of conditions allegedly associated with amalgam, multiple sclerosis had an adjusted hazard ratio (HR) of 1.24 (95% CI: 0.99, 1.53, P = 0.06), but there was no association with chronic fatigue syndrome (HR = 0.98, 95% CI: 0.94, 1.03), or kidney diseases. There were insufficient cases for investigation of Alzheimer's or Parkinson's diseases. Conclusions Results were generally reassuring, and provide only limited evidence of an association between amalgam and disease. Further follow-up of the cohort will permit investigation of diseases more common in the elderly.

Benti R, Canesi M, De Notaris R, Antonini A, Marotta G, Carletto M, Schavini M, Pezzoli G, Gerundini P. 2004. 123I-Ioflupane SPET assessment of dopaminergic striatal damage after long-term exposure to hydrocarbon-solvents in Parkinson's Disease (PD). European Journal of Nuclear Medicine

and Molecular Imaging 31:S247.

Bieganowska ML, Petruczynik A, Doraczynskaszopa A. 1993. Comparison of the retention behavior of some basic drugs used mainly against parkinsons-disease in normal-phase and reversed-phase thin-layer chromatography. Chemia Analityczna 38(6):719-731.
Abstract: R(F) values of some antiparkinsonian drugs have been determined by normal- and reverse-phase thin-layer chromatography. Retention and separation selectivity were controlled by changes in either solvent modifier or adsorbent. The influence of these changes on retention and selectivity (DELTAR(M) values) is presented as chromatographic ''spectra'' by plotting the R(M) values against the mobile phase composition or as regression constants calculated by the least squares method from the equation R(M) = const - mlog C (%) (const = R(M) at 1% C for narmal phase) and from the equation R(M) = const - mC (%) (reversed phase, const = R(Mw) for pure water at 0% modifier); m is the slope of the linear plot.

Block F, Schwarz M. 1998. Global ischemic neuronal damage relates to behavioural deficits: A pharmacological approach. Neuroscience 82(3): 791-803.
Abstract: Global cerebral ischemia leads morphologically to selective neuronal damage in the CAI sector of the hippocampus and in the striatum and functionally to a deficit in spatial learning and memory in the water maze. The results of earlier studies which examined the relationship between neuronal damage and the deficits in the water maze were not clear cut. It has been observed, however, that neuroprotection reduces both the deficits in the water maze as well as the neuronal damage. The present study therefore approached the relationship between the neuronal damage and the deficits in water maze using pharmacological means. Global cerebral ischemia was induced in male Wistar rats by four-vessel occlusion for 20 min. Ischemic rats were treated with the N-methyl-D-aspartate receptor antagonist dextromethorphan, 50 mg/kg, with the calcium antagonist levemopamil, 30 mg/kg, with the radical scavenger EPC-K1, 10 mg/kg, or with solvent. Treatment with dextromethorphan or levemopamil reduced the deficit in spatial learning by limiting the increase in swim distance due to ischemia. Both substances also reduced the deficit in spatial memory by minimizing the ischemia-induced reduction in lime spent in the quadrant of the former platform postion during the probe trial. EPC-KI had no influence on the ischemia-induced behavioural changes. Group comparisons demonstrated that the swim speed and the percentage of the swimming path along the sidewall were affected neither by ischemia nor by any of the treatments. Histological examination revealed neuronal damage in the hippocampus and in the striatum in all of the ischemic rats. Treatment with dextromethorphan or levemopamil reduced the hippocampal damage by 32% and 36%, respectively. Ln addition, dextromethorphan diminished the striatal damage about 78%. Correlation analysis demonstrated a correlation between the cumulative swim distance of all 20 escape trials and hippocampal damage ($r = 0.65$, $P<0.001$) but not between swim distance and striatal damage ($r = 0.14$, $P=0.364$). No correlation was found between quadrant time of the probe trial and either hippocampal damage ($r = -0.21$, $P=0.19$) or striatal damage ($r = -0.02$, $P=0.889$). The average percent age of the swimming path along the side wall related to the hippocampal damage ($r = 0.28$, $P=0.035$) but not to the striatal damage ($r = 0.05$, $P=0.381$). With respect to the average swim speed a correlation to striatal damage was observed ($r = -0.69$, $P<0.001$) but not to hippocampal damage ($r = -0.15$, $P=0.168$). These results clearly demonstrate that using the pharmacological approach it is possible to uncover certain correlations between functional deficits in the water maze and neuronal damage which are both due to global cerebral ischemia. (C) 1997 IBRO. Published by Elsevier Science Ltd.

Blotcky AJ, Claassen JP, Fung YK, Meade AG, Rack EP. 1995. Optimization of procedures for hg-203 instrumental neutron-activation analysis in human urine. Journal of Radioanalytical and Nuclear Chemistry-Articles 195(1):

109-116.
Abstract: Mercury, a known neurotoxin, has been implicated in the etiology and pathogenesis of such disease states as Alzheimer's and Parkinson's diseases. There is concern that the exposure to mercury vapor released from dental amalgam restorations is a potential health hazard. Measurement of mercury concentrations in blood or urine may be useful in diagnosis of mercury poisoning and in assessing the extent of exposure. This study describes the optimization of pre-neutron activation analysis procedures such as sampling, selection of irradiation and counting vials and acid digestion in order to minimize mercury loss via volatilization and/ or permeation through containers. Therefore, the determination of mercury can be complicated by these potential losses. In the optimized procedure 20 mL of urine was spiked with three different concentrations of mercury, digested with concentrated nitric acid and placed in Analysis was performed by subtracting the Se-75 photopeak contribution to the 279 keV Hg-203 photopeak and applying the method of standard additions. Urinary mercury concentrations in normal human subjects were determined to be of the order of 10 ng/mL.

Blum M, Wu G, Mudo G, Belluardo N, Andersson K, Agnati LF, Fuxe K. 1996. Chronic continuous infusion of (-)nicotine reduces basic fibroblast growth factor messenger RNA levels in the ventral midbrain of the intact but not of the 6-hydroxydopamine-lesioned rat. Neuroscience 70(1):169-177.
Abstract: A negative correlation has been found between smoking and Parkinson's disease. There is evidence to Suggest that this correlation appears to be associated with a neuroprotective role of nicotine for dopamine neurons at least in relation to mechanical injury. However, 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP) neurotoxicity to dopamine neurons is enhanced by chronic continuous (-)nicotine. More recently, basic fibroblast growth factor has been found to possess neurotrophic activities for many nerve cells including the dopamine cells in vivo and in vitro. Therefore, it is of interest to explore a possible effect of nicotine on basic fibroblast growth factor expression in the ventral midbrain of intact and 6-hydroxydopamine-lesioned rats and how treatment with nicotine can alter the 6-hydroxydopamine-induced injury of the nigral dopamine nerve cells as evaluated by dopamine biochemistry. In the present paper, an analysis of the effects of chronic continuous infusion of (-)nicotine via minipumps was carried out on basic fibroblast growth factor expression in the vental midbrain of the intact male rat and of the 6-hydroxydopamine lesioned rat. A quantitative messenger RNA protection assay analysis was used as well as an immunocytochemical analysis in the substantia nigra. Our findings give evidence that a two-week continuous infusion with (-)nicotine in the intact rat leads to substantial and dose-related (0.03-0.3 mg/kg per h) reductions of basic fibroblast growth factor messenger RNA levels in the ventral midbrain. These changes are not associated with changes in neuronal and glial basic fibroblast growth factor immunoreactivity in this region with the antibodies used. However, a one-week continuous infusion with (-)nicotine (0.125 mg/kg per h) failed to significantly alter the basic fibroblast growth factor messenger RNA levels in the ventral midbrain of solvent and 6-hydroxydopamine-injected rats and thus also the 6-hydroxydopamine-induced increase of basic fibroblast growth factor messenger RNA levels in the ventral midbrain of the lesioned side observed at this time-interval and known to be of astroglial origin [Chadi G. et al. (1994) Neuroscience 61, 891-910]. In agreement, the 6-hydroxydopamine-induced depletion of dopamine in the neostriatum was unaltered by the nicotine treatment (0.125 mg/kg per h). Thus, chronic continuous (-)nicotine treatment may lead to a reduced basic fibroblast growth factor trophic tone in the ventral midbrain of the intact but not of the 6-hydroxydopamine-lesioned rat neither on the lesioned nor on the unlesioned side of the ventral midbrain. It seems possible that chronic nicotine treatment mainly reduces basic fibroblast growth factor messenger RNA levels of neuronal origin, since the astroglial messenger RNA levels dominate after the 6-hydroxydopamine-induced lesions.

Bodles AM, Guthrie DJS, Greer B, Irvine GB. 2001. Identification of the region of

non-A beta component (NAC) of Alzheimer's disease amyloid responsible for its aggregation and toxicity. J Neurochem 78(2):384-395.
Abstract: The non-beta-amyloid (A beta) component of Alzheimer's disease amyloid (NAC) and its precursor alpha -synuclein have been linked to amyloidogenesis in several neurodegenerative diseases. NAC and alpha -synuclein both form beta -sheet structures upon ageing, aggregate to form fibrils, and are neurotoxic. We recently established that a peptide comprising residues 3-18 of NAC retains these properties. To pinpoint the exact region responsible we have carried out assays of toxicity and physicochemical properties on smaller fragments of NAG. Toxicity was measured by the ability of fresh and aged peptides to inhibit the reduction of the redox dye 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) by rat pheochromocytoma PC12 cells and human neuroblastoma SHSY-5Y cells. On immediate dissolution, or after ageing, the fragments NAC(8-18) and NAC(8-16) are toxic, whereas NAC(12-18), NAC(9-16) and NAC(8-15) are not, Circular dichroism indicates that none of the peptides displays beta -sheet structure; rather all remain random coil throughout 24 h. However, in acetonitrile, an organic solvent known to induce beta sheet, fragments NAC(8-18) and NAC(8-16) both form beta -sheet structure. Only NAC(8-18) aggregates, as indicated by concentration of peptide remaining in solution after 3 days, and forms fibrils, as determined by electron microscopy, These findings indicate that residues 8-16 of NAG, equivalent to residues 68-76 in alpha -synuclein, comprise the region crucial for toxicity.

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.

Bringmann G, Feineis D, God R, Fahr S, Wesemann W, Clement HW, Grote C, Kolasiewicz W, Sontag KH, Heim C, Sontag TA, Reichmann H, Janetzky B, Rausch WD, Abdelmohsen M, Koutsilieri E, Gotz ME, Gsell W, Zielke B, Riederer P. 1996. Neurotoxic effects on the dopaminergic system induced by TaClo (1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline), a potential mammalian alkaloid: In vivo and in vitro studies. Biogenic Amines 12(2): 83-102.
Abstract: Due to their structural analogy to the dopaminergic neurotoxin MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), beta-carbolines are discussed as potential natural inducers of Parkinson's disease (PD). In this paper, we report that the highly chlorinated compound ''TaClo'' (1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline) causes neurodegeneration of the dopaminergic system as demonstrated by in vivo analysis of nigrostriatal dopamine metabolism and by behavioural activities of rats as well as by histochemical examination of mouse brain tissue cultures and brain slices of TaClo treated rats. Furthermore, TaClo exhibits a strong inhibition of complex I of the mitochondrial respiratory chain. Since tryptamine ('Ta') readily reacts with chloral hydrate ('Clo') to give 'TaClo' even under mild quasi-physiological conditions (buffered water, pH 7.4, 37 degrees C), a spontaneous formation of this heterocycle in man has to be taken into consideration after application of the drug chloral hydrate or after exposure to the solvent trichloroethylene ('tri'). Indeed, TaClo was demonstrated to originate in rats after administration of its putative precursors.

Bringmann G, Friedrich H, Feineis D. 1992. Trichloroharmanes as potential endogenously formed inducers of Morbus Parkinson: synthesis, analytics, and first in vivo-investigations. J Neural Transm Suppl 38:15-26.
Abstract: The hypnotic chloral reacts chemically with tryptamine and tryptophan under physiological conditions to give novel trichloro-tetrahydroharmanes ("TTHs"). These are structurally similar to the classical neurotoxin MPTP. Moreover, the TTH-precursor chloral is also a metabolite of the frequently used solvent trichloroethylene (Tri). These properties and first hints at a neuropharmacological potential of this class of substances warrent investigations whether TTHs and other chloral-derived harmanes are formed endogenously and possibly have to do with the pathogenesis of Morbus Parkinson (MP). For an investigation of these problems, some fundamental methods and results had to be elaborated first: the synthesis of several representatives of this novel class of trichloroharmanes, sensitive analytical methods for the detection of these compounds even in biological matrices, and studies concerning their biological "fate".

Bringmann G, God R, Fahr S, Feineis D, Fornadi K, Fornadi F. 1999 May 15. Identification of the dopaminergic neurotoxin 1-trichloromethyl-1,2, 3,4-tetrahydro-beta-carboline in human blood after intake of the hypnotic chloral hydrate. Anal Biochem 270(1):167-75.
Abstract: 1-Trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo), a potent toxin toward dopaminergic neurons, readily originates in vitro from the biogenic amine tryptamine and the unnatural aldehyde chloral. For this reason, this heterocycle has been postulated to be formed endogenously in humans after administration of the hypnotic chloral hydrate or after exposure to the industrial solvent trichloroethylene by a spontaneous chemical ring closure reaction. In this paper, we report on the first identification of TaClo in blood samples of patients treated orally with chloral hydrate. Using a specific and sensitive gas chromatographic screening procedure based upon electron-capture and mass-selective detection, TaClo was determined after conversion to its volatile trifluoroacetyl derivative. The identity of TaClo in humans was clearly demonstrated by GC-MS analysis in selected-ion-monitoring mode, by the

characteristic chlorine isotopic pattern of the molecular ion.

Bringmann G, God R, Feineis D, Wesemann W, Riederer P, Rausch WD, Reichmann H, Sontag KH. 1995. The TaClo concept: 1-Trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo), a new toxin for dopaminergic neurons. Journal of Neural Transmission-Supplement (46): 235-244.
Abstract: Due to its structural analogy to the neurotoxin MPTP, ''TaClo'' (1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline), a compound readily originating in vitro from tryptamine (''Ta'') and chloral (''Clo''), is discussed as a potential natural inducer of parkinsonian-like symptoms. Its spontaneous formation in man has to be taken into account after application of the drug chloral hydrate or after exposure to the solvent trichloroethylene. This first representative of chloral-derived heterocycles could now indeed be demonstrated to be formed in vivo after application of its putative precursors to rats. In vivo analysis of the nigrostriatal dopamine metabolism, behavioural studies, and histochemical findings as well as a strong inhibition of the complex I of the mitochondrial respiratory chain revealed the neurotoxic potential of TaClo on the dopaminergic system.

Buzio L, De Palma G, Mozzoni P, Negrotti A, Scaglioni A, Calzetti S. 2002. Early onset of Parkinson's disease among subjects professionally exposed to either solvents or metals. Mov Disord 17:S144.

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.

Callaway JC, Gynther J, Poso A, Vepsalainen J, Airaksinen MM. 1994. The pictet-spengler reaction and biogenic tryptamines - formation of tetrahydro-beta-carbolines at physiological ph. Journal of Heterocyclic Chemistry 31(2): 431-435.
Abstract: Biogenic tryptamines 1a-c were reacted with aldehydes 2a & b and alpha-keto acids 2c & d to form 1,2,3,4-tetrahydro-beta-carbolines (THBCs) 4d-i, and other products, in a buffered solution at 37-degrees and pH 7.4. These reactions were followed over time by H-1 nmr through integral changes in discrete signals in the spectra. Reactions between tryptamines and acetaldehyde (2b) gave the expected 1-methyl-THBCs 4d-f, while those with sodium glyoxylate (2c) resulted in THBC-1-carboxylic acids 4g-i. Surprisingly, reactions with sodium pyruvate (2d) or formaldehyde (2a) did not form the expected products 4a-c or 4j-1, respectively under these conditions. In successful reactions, 5-methoxytryptamine (1c) was found to be more reactive than tryptamine (1a) or serotonin (1b). MOPAC calculations were employed to investigate reaction intermediates. These results are applicable in research related to aberrant tryptamine metabolism; e.g. depression and alcoholism.

Canesi M, Benti R, De Notaris R, Antonini A, Pezzoli G. 2004. Severe striatal damage after long-term exposure to hydrocarbon-solvents: DATScan data in patients with Parkinson's disease. Mov Disord 19:S189.

Canesi M, Perbellini L, Maestri L, Silvani A, Zecca L, Bet L, Pezzoli G. 2003. Poor metabolization of n-hexane in Parkinson's disease. J Neurol 250(5): 556-560.
Abstract: Although genomic screening studies have identified several genes associated with Parkinson's disease (PD), there is evidence that environmental factors are also involved in the pathogenesis of the disease and that hydrocarbon-solvents may be one of them. The genetic component is less evident in late-onset PD. To assess whether age and PD may affect the catabolism of the hydrocarbon n-hexane, a two-part study was performed. In the first part the urinary levels of its main metabolites, 2,5-hexanedione and 2,5-dimethylpyrroles, were measured in 108 patients and 108 healthy controls, matched by age and sex. Metabolite urinary excretion was significantly reduced in PD patients as compared with controls and was inversely related to age in both groups. In the second part the same comparison was made between 24 non-smoking and 10 smoking patients, matched to controls, after smoking of a hydrocarbon-rich cigarette. in these subjects also n-hexane and 2,5-hexanedione blood levels were measured. There was no appreciable difference in n-hexane blood levels between patients and controls in non-smokers, whereas there was a significant increase in patients over controls in smokers ($p < 0.01$). 2,5-hexanedione blood levels were significantly lower in patients than in healthy controls, both in non-smokers and in smokers, but the reduction was more pronounced in smokers (-46.3% versus - 10.7%). The same was true for 2,5-hexanedione and 2,5-dimethylpyrrole urinary levels. This study suggests that aging and PD may be associated with a reduction in the capacity to eliminate the hydrocarbon n-hexane. This metabolic alteration may play a role in the pathogenesis of PD.

Cashman JR. 1987 Feb. Mutagenicity of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and its metabolites. Toxicology 43(2):173-82.
Abstract: The by-product from a "synthetic heroin" is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a chemical contaminant found to produce neurotoxicity similar to Parkinsonism in susceptible animals. MPTP and its oxidative metabolites were tested in the Salmonella mutagenicity test. Strains of Salmonella typhimurium that carry a nonsense mutation at the site of reversion detect a variety of naturally occurring and direct-acting mutagens. TA 100 is reverted by MPDP+ (1-methyl-4-phenyl-2,3-dihydropyridinium species). This strain is more sensitive to MPDP+

mutagenesis than any other available strain of Salmonella and MPDP+ is considerably more mutagenic than MPTP and other oxidative metabolites including MPTP N-oxide or MPP+ (1-methyl-4-phenylpyridinium ion). Mutagenicity studies of metabolic incubates of MPTP with monoamine oxidase (MAO) suggest the involvement of metabolic bioactivation in the mutagenicity of MPTP. Since MPDP+ is generated from MPTP by MAO and since iminium ions are generated during cellular metabolism, they may make a contribution to the risk of human cancer.

Chancellor AM, Slattery JM, Fraser H, Warlow CP. 1993. Risk-factors for motor-neuron disease - a case-control study based on patients from the scottish-motor-neuron-disease-register. J Neurol Neurosurg Psychiatry 56(11): 1200-1206.
Abstract: In order to identify risk factors for the subsequent development of motor neuron disease (MND) we have carried out a case-control study of incident patients in Scotland, identified using the Scottish Motor Neuron Disease Register. A standard questionnaire was given to 103 patients and the same number of community controls matched on a one to one basis using the general practitioner's (GP) age and sex register. Recall bias was minimised by using GP records to verify the subject's report. There was an overall lifetime excess of fractures in patients, odds ratio (OR) = 1.3 (95% confidence interval (CI), 0.7-2.5) and this was highest in the 5 years before symptom onset (OR = 15, 95% CI, 3.3-654). There was no association with non-fracture trauma but the OR for a manual occupation in patients was 2.6 (95% CI, 1.1-6.3). Both occupational exposure to lead (OR = 5.7, 95% CI, 1-6.30) and solvents/chemicals (OR = 3-3, 95% CI 1.3-10) were significantly more common in patients. No consistent association was found between MND and factors reflecting socioeconomic deprivation in childhood; childhood infections or social class. Our results identify a number of different factors which may contribute to the aetiology of MND.

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.

Cintra A, Andbjer B, Finnman UB, Hagman M, Agnati LF, Hoglund G, Fuxe K. 1996. Subacute toluene exposure increases DA dysfunction in the 6-OH dopamine lesioned nigrostriatal dopaminergic system of the rat. Neurosci Lett 217(1):61-65.
Abstract: The potential neurotoxicity of the solvent toluene to the nigrostriatal dopaminergic system was assessed in a rat model of Parkinson's disease. Rats, 1 day after a unilateral injection of 6-

hydroxydopamine (6-OH DA) into the substantia nigra, inhaled air or different concentrations of toluene (80, 300 or 1000 ppm), 6 h/day for 3 days. The animals were sacrificed 2 days after the last exposure and biochemical measurements of catecholamines and 3,4-dihydroxyphenylacetic acid (DOPAC) were performed in the neostriatum and substantia nigra. Toluene at 80 and 1000 ppm significantly enhanced the depletion of striatal DOPAC levels induced by the lesion and produced at 80 and 300 ppm a trend for intensifying the 6-OH DA-induced depletion of striatal DA stores. The alterations induced after the combined challenge to the dopaminergic nigrostriatal system may reflect endangering actions of toluene.

Collins MA. 2002. Alkaloids, alcohol and Parkinson's disease. Parkinsonism & Related Disorders 8(6):417-422.
Abstract: Relatively early seminal investigations on 'mammalian alkaloid biosynthesis'-endogenous Pictet-Spengler condensations of catecholamines or indoleamines with aldehydes (such as acetaldehyde from ethanol metabolism) to form tetrahydroisoquinoline or beta-carboline alkaloids-and the roles of mammalian alkaloids in the CNS complications of chronic alcoholism were launched in Gerald Cohen's laboratory. While occasional studies on alcohol and the alkaloids continue today, the field of study has been expanded principally by others into Parkinson's disease. Certain mammalian or xenobiotic alkaloids have been examined by various laboratories as possible neurotoxic factors inducing mitochondrial energy depletion and/or oxidative stress in the nigrostriatum. In that regard, specific arguments for N-methylated 'MPP+-like' cationic alkaloids that can be generated centrally from beta-carbolines derived from the environment and diet are summarized. (C) 2002 Elsevier Science Ltd. All rights reserved.

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.

Collins MA, Neafsey EJ, Matsubara K, Cobuzzi RJ, Rollema H. 1992. Indole-n-methylated beta-carbolinium ions as potential brain-bioactivated neurotoxins. Brain Res 570(1-2):154-160.
Abstract: N-Methyl-4-phenylpyridinium ion (MPP+), a highly toxic metabolite produced in the brain from a street drug contaminant, is selectively taken up by nigrostriatal dopaminergic neurons and accumulated intraneuronally in mitochondria. There it inhibits respiration, causes neuronal death and, in primates, provokes a parkinsonian condition. It has been suggested that endogenously generated or activated agents resembling MPP+ may contribute to the development of Parkinson's disease. We report here that simple beta-carbolines derived from tryptophan or related open chain indoles, when specifically methyl-substituted on both (2[beta] and 9[indole]) available nitrogens, display mitochondrial inhibitory potencies and neurotoxic effects in vitro (PC12 cultures) and in vivo (striatal microdialysis) which approach or even surpass MPP+. These results take on physiological significance with our finding that brain enzyme activity catalyzes S-adenosylmethionine-dependent methylations of the beta- and indole-nitrogens in beta-carbolines that have been detected in vivo. The unusual 9[indole]-N-methyl transfer, previously unrecognized in animals, apparently requires

prior methylation of the 2[beta]-nitrogen. Sequential di-N-methylation of endogenous or xenobiotic beta-carbolines to form unique, neurotoxic 2,9-N,N'-dimethyl-beta-carbolinium ions may serve as a brain bioactivation route in chronic neurodegenerative conditions such as Parkinson's disease.

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.

Corsini GU, Zuddas A, Bonuccelli U, Schinelli S, Kopin IJ. 1987 Mar 2. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in mice is enhanced by ethanol or acetaldehyde. Life Sci 40(9):827-32.
Abstract: Persistent neurochemical changes consistent with parkinsonism

have been reported in brains of mice treated with repeated high doses of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). We now report that ethanol or acetaldehyde potentiate MPTP-induced damage to mouse striatum. One hour after the combined treatments (ethanol and MPTP or acetaldehyde and MPTP), the animals exhibited a marked and long-lasting catatonic posture and then returned gradually to apparently normal locomotion. Seven days after MPTP administration, depletion of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in mouse striatum were further potentiated in the group of animals treated with ethanol. This effect was more evident when the treatment was repeated twice and was dose-dependent. Acetaldehyde was more potent than ethanol in enhancing MPTP neurotoxicity. A single exposure to acetaldehyde before and during MPTP treatment produced a very consistent fall of DA, DOPAC and HVA but not serotonin (5HT) or 5-hydroxyindoleacetic acid (5HIAA) in the striatum. This suggests that ethanol effects on MPTP neurotoxicity might be related to acetaldehyde formation.

De Gaspari D, Canesi M, Siri C, Pezzoli G. 2004. Neuropsychological study in patients with Parkinson's disease and long-term exposure to hydrocarbon-solvents. Mov Disord 19:S232.

Demirel M, Yazan Y, Muller RH, Kilic F, Bozan B. 2001. Formulation and in vitro-in vivo evaluation of piribedil solid lipid micro- and nanoparticles. J Microencapsul 18(3):359-371.
Abstract: Modification of the dissolution rate and, thus, the enhancement of the bioavailability of a dopaminergic drug, piribedil, which has a low aqueous solubility and short elimination half-life have been the aim in this study. Preparations of micron and submicron particles using solid lipid carriers have been performed for this purpose. For the avoidance of solvent residues resulting from the preparation technique, cold and hot homogenization methods have been used to prepare solid lipid particles. After obtaining an appropriate particle size, piribedil loading and preparation yield by the use of those two methods, various formulations have been prepared with different lipid, drug and surfactant materials. The factors mentioned were found to a? ect properties of the particles, and the release rate was found to be the fastest in acidic medium. Suspensions of pure piribedil and a formulation, selected according to the results obtained from in vitro dissolution and particle size experiments, were compared using tremor tests in mice. The same suspensions were applied perorally to rabbits and bioavailability of the solid lipid particle was found to be higher than the pure piribedil. After an in vitro-in vivo evaluation of piribedil solid lipid particles developed for Parkinson's disease therapy, it has been determined that release rate could be controlled and piribedil bioavailability could be improved.

Dick F, Semple S, Osborne A, Soutar A, Seaton A, Cherrie JW, Walker LG, Haites N. 2002 . Organic solvent exposure, genes, and risk of neuropsychological impairment. Qjm-an International Journal of Medicine 95(6):379-387.
Abstract: Background: Subtle cognitive and neurological impairments have been found in some workers exposed to organic solvents. Whether these effects occur at or below current legal limits for occupational exposure is controversial. Aim: To determine whether occupational solvent exposure is associated with neuropsychological impairment and whether such risk is modified by polymorphisms in the genes for enzymes involved in detoxification. Design: Retrospective case-control analysis. Methods: We studied 78 former dockyard painters and 42 community controls. Individual respiratory and dermal exposures to solvents were estimated. Neuropsychological tests were administered, including paper and pencil tests, tests from the Neurobehavioural Evaluation System (NES2), together with a structured neurological examination and genotyping of polymorphic enzymes involved in detoxification: GSTM1, GSTT1, GSTP1, NAT1, NAT2, SOD1 and CYP1A1. Results: While initial case-control analyses failed to identify any significant differences between symptomatic and asymptomatic painters, in regression analyses increasing solvent exposure

was associated with increasing risk of cognitive impairment, after adjustment for IQ (or age, where appropriate), smoking and alcohol. There was also an association between exposure and reduction in grip strength. There was limited evidence of risk modification by some enzyme polymorphisms. Discussion: This association between increasing intensity of solvent exposure and neuropsychological impairment may be important at current exposure levels in the UK.

Diporzio U, Zuddas A. 1992. Embryonic dopaminergic neuron transplants in mptp lesioned mouse striatum. Neurochem Int 20:S309-S320.
Abstract: The aim of this work is to study CNS development and plasticity, and to study the mechanisms that allow exogenous embryonic dopaminergic neurons to restore transmitter function in the experimental parkinsonism. Recently, we have developed a new method that produces a selective degeneration of the dopaminergic nigrostriatal system in mice by a combined acetaldehyde/MPTP treatment. This procedure results in a selective and irreversible loss of substantia nigra dopaminergic neurons in C57BL mice, while other dopaminergic areas of the brain are spared. MPTP alone results instead only in a temporary, reversible damage of nigro- striatal dopaminergic functions. Embryonic dopaminergic neurons from ventral mesencephalon or hypothalamus are implanted in lesioned or normal right striata or lateral ventricles. The mesencephalic neurons implanted in a lesioned host form a dense network of fibers which establish functional reinnervation of the striatum (or caudate-putamen complex). After several months about the entire striatal parenchyma appears reinnervated; on average, 20% of the grafted mesencephalic dopaminergic cells survive. Implants of embryonic HYP neurons instead, show little or no survival. Moreover, dopaminergic mesencephalic neurons in control non-lesioned animals show a poor development with little fiber outgrowth. These data indicate that interactions between embryonic dopaminergic neurons and adult striatal neurons is specific. They also suggest that this specificity is sustained by trophic and/or tropic factors possibly produced by the lesioned striatum and by putative inhibitory mechanisms of cell migration and neuritic outgrowth.

Dostert P, Strolin Benedetti M, Dordain G, Vernay D. 1989. Enantiomeric composition of urinary salsolinol in parkinsonian patients after Madopar. J Neural Transm Park Dis Dement Sect 1(4):269-78.
Abstract: Urinary salsolinol output had been shown to be lower in Parkinsonian patients than in controls and to increase largely after L-dopa therapy. It had also been established that the R enantiomer of salsolinol is either the predominant or the sole enantiomer present in the urine of healthy subjects. When Madopar was administered to Parkinsonians, the enantiomeric composition of urinary salsolinol showed an S/R ratio around 1. Considering brain and plasma concentrations in dopamine, acetaldehyde and pyruvate, it is suggested that, under physiological conditions, urinary salsolinol should have a central origin in humans. Conversely, urinary salsolinol in Madopar-treated Parkinsonian patients might be predominantly formed at the periphery.

Durlach J, Bac P, Durlach V, Durlach A, Bara M, Guiet-Bara A. 1997. Are age-related neurodegenerative diseases linked with various types of magnesium depletion? Magnes Res 10(4):339-353.
Abstract: Age-related human neurodegenerative diseases are a major social and medical problem. It is therefore logical to take into consideration every theory with an overall approach to neurodegenerative diseases. This environmental proposal relies mainly on data concerning the Western Pacific amyotrophic lateral sclerosis-Parkinsonism-dementia complex (WP ACS-PD) considered as a prototypal human neurodegenerative disease' and on extrapolation from it to the bulk of neurodegenerative diseases (NDD). NDD would be due to an accelerated ageing process in certain populations of neurons due to the noxious synergy of (1) increased environmental slow deleterious factors (such as slow toxins) and of (2) decreased environmental protective factors (Mg deficient intake particularly). First, it was observed that three apparently dissimilar

conditions occurred at extraordinary high rates in the Guam area: motoneuron disease (ALS), Parkinson's disease (P) and Alzheimer's-like dementia (D). Next, several other foci of endemic ALS-PD were found in Asia and Oceania in three Western Pacific population groups. These included the Chamorro people in Mariana Islands (Guam and Rota), the Auyu and Jakai people of West New Guinea and the Japanese residents of the Kii peninsula (Honshu island). The post-Second World War decline of the occurrence of WP ALS-PD in all three high incidence disease foci coupled with the absence of demonstrable heritable or transmissible factors had led to focus the search for the cause of this degenerative disease on nontransmissible environmental factors that are disappearing as the susceptible population groups acculturate to modern way. Epidemiologic study has shown that preference for traditional Chamorro food is the only one of 23 tested variables significantly associated with an increased risk for PD. An early suggestion incriminated the toxic seed of the false sage palm (Cycas circinalis L) which was used in traditional food and medicine. Laboratory investigation of cycad seed revealed the presence of various toxins and particularly of an 'unusual' non protein aminoacid: L-BMAA (beta-N-methylamino-alanine), an excitotoxic aminoacid. This slow toxin presents some structural similarity to another 'unusual' excitotoxic aminoacid: L-BOAA (beta-N-oxalyl-amino-L-alanine), an exogenous neurotoxin present in the grass pea (Lathyrus sativus) whose excessive consumption may cause lathyrism. The excitotoxicity of both L-BMAA and L-BOAA mainly concerns non-NMDA receptors. The neurotoxicity of these aminoacids varies with experimental models failing to induce an experimental model akin to WP ALS-PD or displaying many of the motor-system and behavioral changes of WP ALS-PD. It may be due to the presence of physiological levels of bicarbonate or of various toxic cofactors: bio-organic such as cycasin or inorganic such as pollutant metals e.g. aluminum or manganese, together with the lack of protective factors (e.g. calcium and magnesium deficiencies). Combined Al intoxication with Ca-Mg deficiencies is a reasonable model to investigate the pathogenesis of neurodegenerative diseases and eventually to screen their treatments. It may also be considered as a model of magnesium deficit, but it does not concern simple magnesium deficiency reversible with mere oral physiological magnesium supplementation. Magnesium deficiency cannot result in neurodegenerative disease. Combined Al intoxication with Ca Mg deficiencies is not reversible through physiological oral magnesium supplementation. It therefore constitutes a type of experimental magnesium depletion model, instrumental in the investigation of the pathogenesis of magnesium depletion and in the screening of its still unknown possible treatments. As a rule, no changes have been found in brain magnesium concentrations during the course of magnesium deficiency in adult rats, but in the experimental and clinical type of magnesium depletion related to pollutant metal load combined with low Mg and Ca dietary intake, magnesium concentrations were decreased in various structures of the nervous central system. Ca deficiency plus Al load seems less deleterious than Ca/Mg deficiencies plus Al load and magnesium deficiency plus Al load appears more noxious than Ca/Mg deficiencies plus Al load. Neuronal morphometric alterations were observed only in the low magnesium groups. It is speculated that magnesium depletion, by increasing the Ca/Mg ratio in the CNS tissues, further accelerated the uptake of Al into the CNS which promoted the neurodegenerative processes. Lesser noxiousness of magnesium deficiency when combined with Ca deficiency might be mainly ascribed to a lower increase in cellular calcium. The physiopathological mechanisms of neurodegenerative and neurotoxic insults associate several intricated and interactive factors: e.g. excitotoxicity, depolarization, decreased energy metabolism and cationic gradient, increased Na and Ca cellular influx, oxidant and arachidonic cascades. Magnesium depletion due to systemic kainic acid (KA) plus magnesium deficiency appears as the model most closely linked to the main basic mechanisms of age-related neurological disorders. It associates low dietary magnesium intake (the most noxious decrease in neuroprotective factors) to the most deleterious excitotoxicity

in elderly: kainic acid, an agonist of non-MDA receptors such as L-BMAA and L-BOAA. Relying on these data on endemic WP ALS-PD complex a general environmental theory of the bulk of the age-related neurodegenerative diseases has been hypothetized: NDD would be due to an accelerating ageing process caused by the sum of increased environmental slow deleterious factors and of decreased environmental protective factors (a low magnesium intake particularly). The very value of the environmental pathogenesis of the endemic prototypal neurodegenerative complex is not yet firmly established. Postulated nutritional deficiencies of Ca and Mg have only been inferred from indirect and therefore questionable data. Direct evaluation of Mg, Ca and heavy metal status in patients with ALS-PD and in Chamorro control subjects showed very similar results. It is even more hazardous to extrapolate from physiopathological data concerning endemic WP ALS-PD to sporadic cases,of amyotrophic lateral sclerosis (ALS), Parkinson's disease (P) and dementia of the Alzheimer's type (D). It has never been observed that patients with ALS or P or D had low Ca and Mg dietary intake. In these neurodegenerative diseases investigation of magnesium status disagrees with the hypothesis of magnesium deficiency, but stresses the possible role of some various types of magnesium depletion, with possible aetiopathogenic importance of chronic pollutant metal toxicity. More criticism can be expressed concerning extrapolation from environmental data on WP ALS-PD complex to other degenerative diseases presenting no common symptomatology such as multiple sclerosis or spongiform encephalopathies. From these studies mainly based on endemic WP ALS-PD data, it appears difficult to infer a general environmental scheme of the bulk of neurodegenerative diseases. But they have generated various experimental acquired models of magnesium depletion whose pathogenic mechanisms are linked to those of neurodegenerative diseases, particularly when excitotoxicity and magnesium deficiency were combined. Today, magnesium supplementation carried out with the usual magnesium salts either at physiological or at pharmacological doses appears of little help as a curative treatment of neurodegenerative diseases. It might even be contraindicated in such cases as Alzheimer's disease and multiple sclerosis. But the experimental models of magnesium depletion related to neurodegenerative diseases should constitute promising tools for the screening of effective treatments.

Foppoli C, Coccia R, Blarzino C, Cini C, Rosei MA. 2002. Tetrahydroisoquinoline derivatives of enkephalins: synthesis and properties. Biochem Pharmacol 63(10):1885-1892.
Abstract: Tetrahydroisoquinolines (TIQs) are endogenous alkaloid compounds deriving from the non-enzymatic Pictet-Spengler condensation of catecholamines with aldehydes. These compounds are able to unsettle catecholamines uptake and release from synaptosomes and have been detected in urine and in post-mortem Parkinsonian brains. We have obtained in vitro, by the reaction of dopa-enkephalin (dopa-Gly-Gly-Phe-Leu) with acetaldehyde in the presence of rameic ions, a TIQ derivative of Leu-enkephalin. The isolation and the recovery of the peptide was obtained by HPLC. The acid hydrolysis and the subsequent analysis of the peptide lysate by the Amino acid analyser clearly revealed the absence of dopa, while the electrospray ionisation mass spectrometry showed that the sequence of the enkephalin derivative was the following: 3-carboxy-salsolinol-Gly-Gly-Phe-Leu (TIQ-enkephalin). This compound was not a good substrate for microsomal aminopeptidase and pronase with respect to Leu-enkephalin. Tested in the binding assay, the TIQ-enkephalin exhibited a very poor affinity toward the enkephalin receptors. When the TIQ-enkephalin was incubated with tyrosinase or peroxidase/H2O2, the formation of TIQ-opio-melanins occurred. (C) 2002 Elsevier Science Inc. All rights reserved.

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.

Fredriksson A, Fredriksson M, Eriksson P. 1993 Oct. Neonatal exposure to paraquat or MPTP induces permanent changes in striatum dopamine and behavior in adult mice. Toxicol Appl Pharmacol 122(2):258-64.
Abstract: We have recently reported that environmental toxicants, such as DDT, PCBs, pyrethroids, and nicotine can induce permanent functional and neurochemical changes in adult mice when given to neonatal mice during the peak of rapid brain growth. In the present investigation the neurotoxic effects following neonatal exposure to paraquat (N,N'-dimethyl-4,4'-bipyridylium), a broad-spectrum herbicide with structural similarity to the 1-methyl-4-phenylpyridium ion (MPP+), the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which can induce Parkinson's syndrome, and MPTP were studied. Five groups of mice were given paraquat or MPTP orally: group 1, vehicle; groups 2 and 3, MPTP 0.3 and 20 mg/kg; groups 4 and 5, paraquat 0.07 and 0.36 mg/kg when 10 and 11 days old. Neonatal spontaneous motor activity was tested on Day 18 in mice given paraquat 0.36 mg/kg body wt. Adult spontaneous motor activity testing was performed at ages 60 and 120 days. On Day 125 the mice were decapitated and the contents of dopamine (DA), serotonin (5-HT), and metabolites in striatum were analyzed. The results may be summarized as follows: (1) No signs of acute toxicity or differences in weight gain were observed in any of the groups. Nor was any respiratory distress or motor performance dysfunction evident on Day 18 in mice given paraquat 0.36 mg/kg body wt. (2) The behavioral tests at 60 days of age showed a marked hypoactive condition in the mice given paraquat (at both doses) and MPTP (at both doses). (3) At the age of 120 days the hypoactive behavior persisted and appeared even more pronounced. (4) The high doses of MPTP and paraquat--and to a less extent the low doses--reduced the striatal content of DA and metabolites without affecting 5-HT. The altered behavior, together with the dose-dependent reduction of DA and metabolites in neostriata in this study, further demonstrates the susceptibility to low-dose exposure to environmental pollutants during the neonatal period.

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.

Gerlach M, Xiao AY, Heim C, Lan J, God R, Feineis D, Bringmann G, Riederer P, Sontag KH. 1998. 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline increases extracellular serotonin and stimulates hydroxyl radical production in rats. Neurosci Lett 257(1):17-20.
Abstract: 1-Trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo), a neurotoxin structurally similar to the dopaminergic neurotoxin MPTP, may be formed in humans treated with chloral hydrate or exposed to trichloroethylene, a widely used industrial solvent. Systemically administered TaClo (0.4 mg/kg, i.p.) induced an immediate and transient release of dopamine (DA) and serotonin (5-HT) measured using microdialysis. However, only 5-HT was increased significantly (area under the curve, AUG, for the 1-2 h-period following TaClo administration: 400% compared with the respective control value; 2-3 h-period: 326%). This was followed by a progressive increase in hydroxyl radical formation reflected by higher extracellular concentrations of the hydroxylate product of salicylic acid, 2,3-dihydroxybenzoic acid (AUC for the 1-2 h period following TaClo administration: 182% compared with the respective control value; 2-3 h period: 190%). In contrast, extracellular glutamate and GABA were increased 2-3 h postinjection by 64 and 51%, respectively. These data suggest that TaClo stimulates the generation of hydroxyl free radicals via an acute release of 5-HT and perhaps DA. (C) 1998 Elsevier Science Ireland Ltd. All rights reserved.

Glass GA, DeLisle DM, DeTogni P, Gabig TG, Magee BH, Markert M, Babior BM. 1986 Oct 5. The respiratory burst oxidase of human neutrophils. Further studies of the purified enzyme. J Biol Chem 261(28):13247-51.
Abstract: A superoxide-forming oxidase from activated human neutrophil membranes was solubilized by two slightly different methods, then purified by "dye-affinity" chromatography. Kinetic studies of the purified preparations gave Vmax values of 5-10 mumol of O-2/min/mg of protein, and Km values for NADH and NADPH that were in reasonable agreement with values determined previously using particulate and crude solubilized preparations of the respiratory burst oxidase. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis showed prominent bands at 67, 48, and 32 kDa, together with some minor contaminants, whereas gel electrophoresis under non-denaturing conditions gave a single major band that when eluted and re-electrophoresed in the presence of sodium dodecyl sulfate showed bands at 67, 48, 32 kDa. We believe that all three bands represent oxidase components. The flavin content of the purified enzyme was 20.4 +/- 2.0 S.E. pmol of FAD/microgram of protein, whereas heme averaged 0.1 +/- 0.02 pmol/microgram and ubiquinone could not be detected. Assuming that the enzyme is composed of one 67-kDa subunit, one 48-kDa subunit, and one 32-kDa subunit (i.e. that its molecular mass is approximately 150 kDa), it can be calculated to have a turnover number of 700-1500 min-1, in agreement with a value reported previously for oxidase in a particulate O-2-forming system (Cross, A. R., Parkinson, J. F., and Jones, O. T. G. (1985) Biochem. J. 226, 881-884), and to contain the following quantities of redox carriers (mol/mol): FAD, 3.0; heme, 0.015; ubiquinone, less than 0.06. It remains to be determined whether this preparation represents the complete respiratory burst oxidase or is only the pyridine nucleotide dehydrogenating component of a more complex enzyme.

Guehl D, Bezard E, Dovero S, Boraud T, Bioulac B, Gross C. 1999. Trichloroethylene and parkinsonism: a human and experimental observation. Eur J Neurol 6(5):609-611.

Abstract: This report describes the case of a 47-year-old woman who developed Parkinson's disease after seven years of professional exposure to trichloroethylene. In the light of this clinical report, mice were intoxicated with trichloroethylene and tyrosine hydroxylase immunoreactivity was used to measure neuronal death in the substantia nigra pars compacta. Treated mice presented significant dopaminergic neuronal death in comparison with control mice (50%). The environmental trichlorethylene pollution, as well as other unspecific neurotoxic solvents, could potentially contribute to the genesis of some casts of Parkinson's disease. Eur J Neurol 6:609-611 (C) 1999 Lippincott Williams & Wilkins.

Gunnarsson LG, Bodin L, Soderfeldt B, Axelson O. 1992. A case-control study of motor-neuron disease - its relation to heritability, and occupational exposures, particularly to solvents. Br J Ind Med 49(11):791-798.
Abstract: Motor neurone disease (MND) was studied in relation to various determinants in a case-control study covering nine counties in southern Sweden. A questionnaire about occupational exposures, medical history, lifestyle factors etc was given to all cases in the age range 45-79 and to a random sample of 500 population controls in the same age range. The questionnaires were answered by 92 cases and 372 controls, a response rate of 85% and 75% respectively. Among men high Mantel-Haenszel odds ratios (MHORs) were obtained for electricity work (MHOR = 6.7,95% confidence interval (95% CI) 1.0-32.1), welding (MHOR = 3.7, 95% CI 1.1-13-0), and impregnating agents (MHOR = 3.5, 95% CI 0.9-13.1). Heritability with regard to a neurodegenerative disease or thyroid disease seemed to predispose to a risk of developing MND (OR = 2-1,95% CI 1.0-4.3). The highest OR was found for the combination of such heritability, exposure to solvents, and male sex (OR = 15.6, 95% CI 2.8-87.0), a combination that occurred for seven cases and three controls. Hereditary factors and external exposures had a different distribution among cases with the spinal type of MND than among cases with involvement of the pyramidal tract or bulbar paresis also.

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.

Heap L, Ward RJ, Abiaka C, Dexter D, Lawlor M, Pratt O, Thomson A, Shaw K, Peters TJ. 1995. The influence of brain acetaldehyde on oxidative status, dopamine metabolism and visual-discrimination task. Biochem Pharmacol 50(2):263-270.
Abstract: The toxic effect of acetaldehyde on brain oxidative capacity and dopamine metabolism has been investigated in rat brains after a single intraperitoneal injection of acetaldehyde (5 mmol/kg) and the results compared with those from chronically ethanol fed rats. Acetaldehyde was present in rat brain 120 hr after a single dose of acetaldehyde, confirming that it is able to cross the blood-brain barrier. Brain catalase increased significantly after acetaldehyde or chronic ethanol administration although

there were no other significant changes in the total brain activity of superoxide dismutase, glutathione peroxidase or glutathione reductase. Dopamine turnover was increased in both experimental groups. The acute dose of acetaldehyde reduced the ability of the rats to relearn a computer visual discrimination task.

Heiss WD, Wurker M. 1999. Value of functional imaging in Parkinson's disease and related movement disorders. Nervenarzt 70:S2-S10.
Abstract: Modalities for imaging morphology do not contribute significantly to the differential diagnosis of movement disorders. In contrast, functional imaging as PET or SPECT can differentiate among Parkinson's disease (PD),vascular or toxic Parkinsonism and movement disorders within multi system degeneration. Especially the decreased DOPA uptake - detected by F-18-DOPA or I-123-beta CIT - within the striate with accentuation in the posterior putamen is typical for PD, where initially D2-receptor activity - imaged by C-11-raclopride or I-123-iodobenzamide - is increased. In contrast to this typical pattern dopaminergic terminals as well as D2-receptors are diffusely reduced in multi system degeneration,where often energy metabolism is additionally disturbed. In Parkinson syndrome of vascular origin focal disturbances of pre- and postsynaptic dopaminergic sites and energy metabolism are found, movement disorders after intoxication are accompanied by selective loss of dopaminergic neurons (MPTP) or by widespread neuronal damage in the basal ganglia as well as in the cortex (Cyanide, solvents). Functional studies additionally permit the follow-up of disease progression, by which also the efficacy of therapeutic strategies can be assessed.

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.

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.

Huttenbrink KB. 1995 Nov. [Disorders of the sense of smell and taste]. Ther Umsch 52(11):732-7.
Abstract: Disorders of olfaction and taste are infrequent, but a complete loss of smell or taste reduces the quality of life significantly. The sensitivity of human olfaction is remarkable, even for specific stimuli: Just a few molecules are enough to induce the correct identification of sterilised and ultraheated milk. Olfaction and taste are called 'chemical senses' because in both cases the adequate stimulus consists of molecules that bind to receptors of the sensory cells. The perceptions of smell and taste are often combined. Taste differentiates only four qualities: sweet, sour, salty, and bitter. The typical flavor of food or drink is detected by olfaction. Disturbances of olfaction can be due to respiratory disorders such as nasal polyps, a deviation of the nasal septum or chronic sinusitis. Such conditions can reduce airflow through the olfactory cleft at the roof of the nasal cavity. They can be corrected by modern endoscopic surgery of the nose. Epithelial disorders involving the sensory cells are most often caused by viral infections (influenza-anosmia) or toxic destruction of the sensory epithelium (solvents or gases). Epithelial disorders can be cured only rarely by any treatment. Corticosteroids, zinc, and vitamin A are tried frequently. Neural disorders occur after frontobasal trauma and during neurological diseases such as Parkinson's or Alzheimer's disease. Disorders of olfaction can be an early sign of such neurological diseases and sophisticated examination of this sense can contribute to their early diagnosis. However, no specific treatments have yet been identified. Disorders of taste can be due to toxic, chemical or inflammatory damage to the sensory cells of the tongue.(ABSTRACT TRUNCATED AT 250 WORDS)

Janetzky B, Gille G, Abdel-Mohsen M, God R, Rausch WD, Bringmann G, Reichmann H. 1999. Effect of highly halogenated beta-carbolines on dopaminergic cells in culture and on mitochondrial respiration. Drug Development Research 46(1):51-56.
Abstract: Pyridoindoles (carbolines) are relatively common indole alkaloids in most diets and in our ecosystem. Besides 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its active metabolite, MPP+, several psychotropic beta-carbolines have been described to exhibit neurotoxic effects on the dopaminergic system. In this work, we have investigated a new class of neurotoxic P-carbolines, the highly halogenated tetrahydro-beta-carbolines. The present compounds are derived from the condensation of endogenous tryptamine with the hypnotic drug chloral hydrate or by exposure to the industrial solvent trichloroethylene (which can be metabolized to chloral). These tetrahydro-beta-carbolines inhibit the mitochondrial respiratory chain, acting as strong inhibitors of Complex I and partial inhibitors of Complex II. They are also neurotoxic to dopaminergic neurons in primary cell culture. (C) 1999 Wiley-Liss, Inc.

Jenner P. 1998. Oxidative mechanisms in nigral cell death in Parkinson's disease. Mov Disord 13:24-34.
Abstract: Oxidative stress may contribute to nigral cell death in Parkinson's disease based on postmortem investigations showing increased iron levels, decreased levels of reduced glutathione (GSH), and impaired mitochondrial function. This leads to oxidative damage because lipid peroxidation is increased in substantia nigra and there is a widespread increase in protein and DNA oxidation in the brain in Parkinson's disease. Nitric oxide (NO)

may be one of the free radical species involved in nigral degeneration. NO is involved in the production of hydroxyl radicals resulting from MPP+-induced dopamine efflux in striatum. Mice treated with the neuronal nitric oxide synthase (NOS) inhibitor 7-nitroindazole show reduced toxicity to MPTP and knock-out mice lacking neuronal NOS show decreased MPTP susceptibility. In primates, 7-nitroindazole inhibits MPTP toxicity but this remains controversial because no protection is afforded by the nonspecific NOS inhibitor, L-NAME. Indeed, in Parkinson's disease itself, there is little evidence for nitric oxide's involvement in nigral pathology. A susceptibility factor for the development of Parkinson's disease may involve isoforms of cytochrome P450, some of which are found in the brain. CYP2E1, which is associated with free radical production and the formation of endogenous toxins, is selectively localized in nigral dopamine-containing cells. CYP2E1 metabolizes n-hexane leading to the formation of its neurotoxic metabolite 2,5-hexanedione which may explain cases of solvent-induced parkinsonism. Oxidative processes clearly contribute to the pathology of Parkinson's disease but are probably secondary to some other primary unidentified cause, presumably genetic or environmental. Nevertheless, their involvement may allow therapeutic intervention in the cascade of events associated with the progression of Parkinson's disease.

Jennum P, Hein HO, Suadicani P, Gyntelberg F . 1994. Headache and cognitive dysfunctions in snorers - a cross-sectional study of 3323 men aged 54 to 74 years - the copenhagen male study. Arch Neurol 51(9):937-942.
Abstract: Objective: Cognitive symptoms, headache, and sleep-related complaints, including snoring, are commonly reported by patients with sleep apnea. Because patients with sleep apnea generally are snorers, we decided to study whether snoring per se is associated with cognitive complaints and headache. Design: Cross-sectional epidemiologic follow-up study. Setting: General community. Participants: A total of 3323 men, aged 54 to 74 years, previously selected from among employees of public or private companies in the Copenhagen, Denmark, area. Method: Participants were classified according to self-reported snoring habits and these were compared with self-reported cognitive complaints and headache. Fourteen potential confounders were included. Results: The odds ratio (95% confidence interval) for headache was 1.5 (1.3 to 1.8, P<. 0001) for self-reported snorers after adjustments for age, body mass index, and alcohol and tobacco consumption, whereas no relationships were found between snoring and memory or concentration problems in the total population. Snoring was not related to use of central nervous system medication; previous stroke; presence of parkinsonism, epilepsy, or psychiatric diseases; previous head trauma; or exposure to organic solvents. Hypersomnia was significantly associated with snoring (P<.0001), headache (P<.0001), memory problems (P<.0001), concentration problems (P<.0001), age (P<.01), body mass index (P<.001), and alcohol consumption (P<.05) and negatively correlated with smoking (P<.0001). Irrespective of the severity of hypersomnia, no association was found between snoring and memory or concentration problems. The relationship between snoring and headache was independent of severity of hypersomnia. Conclusions: Snoring is associated with headache but not with cognitive dysfunction. Hypersomnia shows a correlation to cognitive problems. If associations are found between snoring and cognitive dysfunction, these may be related in part to the presence of hypersomnia.

Jung TW, Lee JY, Shim WS, Kang ES, Kim SK, Ahn CW, Lee HC, Cha BS. 2006. Rosiglitazone protects human neuroblastoma SH-SY5Y cells against acetaldehyde-induced cytotoxicity. Biochem Biophys Res Commun 340(1): 221-227.
Abstract: Acetaldehyde, an inhibitor of mitochondrial function, has been widely used as a neurotoxin because it elicits a severe Parkinson's disease-like syndrome with elevation of the intracellular reactive oxygen species level and apoptosis. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, has been known to show various non-hypoglycemic effects, including anti-inflammatory, anti-atherogenic, and anti-apoptotic. In this study, we investigated the protective effects of

rosiglitazone on acetaldehyde-induced apoptosis in human neuroblastoma SH-SY5Y cells and attempted to examine its mechanism. Acetaldehyde-induced apoptosis was moderately reversed by rosiglitazone treatment. Our results suggest that the protective effects of rosiglitazone on acetaldehyde-induced apoptosis may be ascribed to ability to induce the expression of anti-oxidant enzymes and to regulate Bcl-2 and Bax expression. These data indicate that rosiglitazone may provide a useful therapeutic strategy for the prevention of progressive neurodegenerative disease such as Parkinson's disease. (c) 2005 Elsevier Inc. All rights reserved.

Kardos J, Okuno D, Kawai T, Hagihara Y, Yumoto N, Kitagawa T, Zavodszky P, Naiki H, Goto Y. 2005. Structural studies reveal that the diverse morphology of beta(2)-microglobulin aggregates is a reflection of different molecular architectures. Biochimica Et Biophysica Acta-Proteins and Proteomics 1753(1):108-120.
Abstract: Amyloid deposition accompanies over 20 degenerative diseases in human, including Alzheimer's, Parkinson's, and prion diseases. Recent studies revealed the importance of other type of protein aggregates, e.g., non-specific aggregates, protofibrils, and small oligomers in the development of such diseases and proved their increased toxicity for living cells in comparison with mature amyloid fibrils. We carried out a comparative structural analysis of different monomeric and aggregated states of beta 2-microglobulin, a protein responsible for hemodialysis-related amyloidosis. We investigated the structure of the native and acid-denatured states, as well as that of mature fibrils, immature fibrils, amorphous aggregates, and heat-induced filaments, prepared under various in vitro conditions. Infrared spectroscopy demonstrated that the beta-sheet compositions of immature fibrils, heat-induced filaments and amorphous aggregates are characteristic of antiparallel intermolecular beta-sheet structure while mature fibrils are different from all others suggesting a unique overall structure and assembly. Filamentous aggregates prepared by heat treatment are of importance in understanding the in vivo disease because of their stability under physiological conditions, where amyloid fibrils and protofibrils formed at acidic pH depolymerize. Atomic force microscopy of heat-induced filaments represented a morphology similar to that of the low pH immature fibrils. At a pH close to the pI of the protein, amorphous aggregates were formed readily with association of the molecules in native-like conformation, followed by formation of intermolecular beta-sheet structure in a longer time-scale. Extent of the core buried from the solvent in the various states was investigated by H/D exchange of the amide protons. (c) 2005 Elsevier B.V. All rights reserved.

Kaylor J, Bodner N, Edridge S, Yamin G, Hong DP, Fink AL. 2005. Characterization of oligomeric intermediates in alpha-synuclein fibrillation: FRET studies of Y125W/Y133F/Y136F alpha-synuclein. J Mol Biol 353(2):357-372.
Abstract: The aggregation of alpha-synuclein is believed to be a critical step in the etiology of Parkinson's disease. A variety of biophysical techniques were used to investigate the aggregation and fibrillation of alpha-synuclein in which one of the four intrinsic Tyr residues was replaced by Trp, and two others by Phe, in order to permit fluorescence resonance energy transfer (FRET) between residues 39 (Tyr) and 125 (Trp). The mutant Y125W/Y133F/Y136F alpha-synuclein (one Tyr, one Trp) showed fibrillation kinetics similar to that of the wild-type, as did the Y125F/Y133F/Y136F (one Tyr, no Trp) and Y39F/Y125W/Y133F/Y136F (no Tyr, one Trp) mutants. Time-dependent changes in FRET, Fourier transform infrared, Trp fluorescence, dynamic light-scattering and other probes, indicate the existence of a transient oligomer, whose population reaches a maximum at the end of the lag time. This oligomer, in which the alpha-synuclein is in a partially folded conformation, is subsequently converted into fibrils, and has physical properties that are distinct from those of the monomer and fibrils. In addition, another population of soluble oligomers was observed to coexist with fibrils at completion of the reaction. The average distance between Tyr39 and Trp125 decreases from 24.9 angstrom in the monomer

to 21.9 angstrom in the early oligomer and 18.8 angstrom in the late oligomer. Trp125 remains solvent-exposed in both the oligomers and fibrils, indicating that the C-terminal domain is not part of the fibril core. No FRET was observed in the fibrils, due to quenching of Tyr39 fluorescence in the fibril core. Thus, aggregation of alpha-synuclein involves multiple oligomeric intermediates and competing pathways. (c) 2005 Elsevier Ltd. All rights reserved.

Kennedy JH. 1997. HPLC purification of pergolide using silica gel. Organic Process Research & Development 1(1):68-71.
Abstract: pergolide is a synthetic ergot alkaloid approved for the treatment of Parkinson's disease. Process-related impurities from the synthesis are difficult to remove chemically without significant yield loss. An alternative purification procedure was necessary. Pergolide is soluble in nonaqueous solvents such as chloroform, methylene chloride, and dimethylformamide. Solubility is improved when the halocarbon is mixed with an alcohol such as methanol. These characteristics are desirable for silica gel chromatography. This paper describes the evaluation of solubility as a function of halocarbon and the development of a silica gel system to separate the process-related impurities from pergolide. The criteria for choosing a commercially available silica gel and results from purification using axial compression column technology are also discussed.

Kidd PM. 2005 Dec. Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management. Altern Med Rev 10(4):268-93.
Abstract: Degenerative brain disorders (neurodegeneration) can be frustrating for both conventional and alternative practitioners. A more comprehensive, integrative approach is urgently needed. One emerging focus for intervention is brain energetics. Specifically, mitochondrial insufficiency contributes to the etiopathology of many such disorders. Electron leakages inherent to mitochondrial energetics generate reactive oxygen free radical species that may place the ultimate limit on lifespan. Exogenous toxins, such as mercury and other environmental contaminants, exacerbate mitochondrial electron leakage, hastening their demise and that of their host cells. Studies of the brain in Alzheimer's and other dementias, Down syndrome, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Friedreich's ataxia, aging, and constitutive disorders demonstrate impairments of the mitochondrial citric acid cycle and oxidative phosphorylation (OXPHOS) enzymes. Imaging or metabolic assays frequently reveal energetic insufficiency and depleted energy reserve in brain tissue in situ. Orthomolecular nutrients involved in mitochondrial metabolism provide clinical benefit. Among these are the essential minerals and the B vitamin group; vitamins E and K; and the antioxidant and energetic cofactors alpha-lipoic acid (ALA), ubiquinone (coenzyme Q10; CoQ10), and nicotinamide adenine dinucleotide, reduced (NADH). Recent advances in the area of stem cells and growth factors encourage optimism regarding brain regeneration. The trophic nutrients acetyl L-carnitine (ALCAR), glycerophosphocholine (GPC), and phosphatidylserine (PS) provide mitochondrial support and conserve growth factor receptors; all three improved cognition in double-blind trials. The omega-3 fatty acid docosahexaenoic acid (DHA) is enzymatically combined with GPC and PS to form membrane phospholipids for nerve cell expansion. Practical recommendations are presented for integrating these safe and well-tolerated orthomolecular nutrients into a comprehensive dietary supplementation program for brain vitality and productive lifespan.

Kim TD, Paik SR, Yang CH, Kim J. 2000. Structural changes in alpha-synuclein affect its chaperone-like activity in vitro. Protein Sci 9(12):2489-2496.
Abstract: alpha -Synuclein, a major constituent of Lewy bodies (LBs) in Parkinson's disease (PD), has been implicated to play a critical role in synaptic events, such as neuronal plasticity during development, learning, and degeneration under pathological conditions, although the physiological function of alpha -synuclein has not yet been established. We here present

biochemical evidence that recombinant alpha -synuclein has a chaperone-like function against thermal and chemical stress in vitro. In our experiments, alpha -synuclein protected glutathione S-transferase (GST) and aldolase from heat-induced precipitation, and alpha -lactalbumin and bovine serum albumin from dithiothreitol (DTT)-induced precipitation like other molecular chaperones. Moreover, preheating of alpha -synuclein, which is believed to reorganize the molecular surface of alpha -synuclein, increased the chaperone-like activity. Interestingly, in organic solvents, which promotes the formation of secondary structure, alpha -synuclein aggregated more easily than in its native condition, which eventually might abrogate the chaperone-like function of the protein. In addition, alpha -synuclein was also rapidly and significantly precipitated by heat in the presence of Zn2+ in vitro, whereas it was not affected by the presence of Ca2+ or Mg2+. Circular dichroism spectra confirmed that alpha -synuclein underwent conformational change in the presence of Zn2+. Taken together, our data suggest that alpha -synuclein could act as a molecular chaperone, and that the conformational change of the alpha -synuclein could explain the aggregation kinetics of alpha -synuclein, which may be related to the abolishment of the chaperonic-like activity.

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.

Kochen W, Kohlmuller D, De Biasi P, Ramsay R . 2003. The Endogeneous Formation of Highly Chlorinated Tetrahydro-Beta-Carbolines as a Possible Causative Mechanism in Idiopathic Parkinson's DiseaseVolume 527. p 253-263. Developments in Tryptophan and Serotonin Metabolism: Advances in Experimental Medicine and Biology.
Abstract: The causative interrelationship between long-term, low level exposure to chlorinated volatile organic solvents (VOSs) and neurodegenerative diseases (polyneuropathy, encephalopathy) are still an issue of controversial debate. Endogeneously formed chlorinated tetrahydro-beta-carbolims found by Bringmann 1995 (TaClo hypothesis)

may contribute, in particular, to the development of (idiopathic) Parkinson's disease (PD) in the presence of the sufficient amount of trichloroacetaldehyde, an intermediate in metabolism of trichloroethylene (TRI). Long-term storage of specific VOSs over years, evident frrom exhalation pattern during the postexposure period, may serve as a promoting factor to form continuously TaClo non-enzymatically from tryptamine and trichloroacetaldehyde. Thus, the induction of TaClo-mediated neurotoxic processes extends over years. The onset of Parkinson's disease in three chronic TRI-exposed individuals during the postexposure period could be associated with the presence of TaClo in ng-range. Consequently, determination of TaClo and its derivatives in blood of humans exposed to chlorinated VOSs may serve as a marker of risk indicating either causative or supportive processes of neurodegeneration that may lead to manifestation of PD after many years.

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.

Kondo I, Yamamoto M. 1998. Genetic polymorphism of paraoxonase 1 (PON1) and susceptibility to Parkinson's disease. Brain Res 806(2):271-273.
Abstract: Toxicologists have thought that the paraoxonase (PON) enzyme polymorphism might contribute to effects of pollutants and other environmental chemicals on susceptibility to cancer, birth defects and Parkinson's disease (PD). We studied a biallelic PON1 polymorphism at codon 192 (A and B alleles) in 166 patients with sporadic idiopathic PD. The frequency of the B (Arg) allele of PON1 was significantly increased in patients with PD than in healthy controls (chi(2) = 8.75, df= 1, P < 0.005). The relative risk of PD in homozygotes for the B allele was 1.60 fold higher than individuals with the A (Gln) allele (chi(2) = 7.38, df= 1, P < 0.01). Our data suggest that environmental neurotoxins metabolized by PON1 might be responsible for neurodegeneration with aging and that the B (Arg) allele form might have genetic susceptibility to PD. (C) 1998 Elsevier Science B.V. All rights reserved.

Kopin IJ. 1987. Mptp - an industrial-chemical and contaminant of illicit narcotics stimulates a new era in research on parkinsons-disease. Environ Health Perspect 75:45-51.

Kordysh EA, Herishanu Y, Goldsmith JR. 1997. Chemical exposures and Parkinson's disease in residents of three Negev kibbutzim. Environ Res 73 (1-2):162-165.
Abstract: We consider whether chemical pollutants in drinking water (including aromatic hydrocarbons, alkanes, halogenated aliphatic hydrocarbons, and phthalic acid) or used occupationally in agriculture that have shown no parkinsonism-inducing effect may be responsible for excess cases of Parkinson's disease (PD) in three adjacent kibbutzim in southern Israel (Negev). Literature data on PD pathogenesis have been

compared with common pathogenetic pathways to xenobiotics effects; the following neurotoxic mechanisms, besides individual sensitivity, have been suggested: (1) impairment of the protective role of the substantia nigra against toxicants by binding of chemicals to melanin; (2) oxidative stress induction, including glutathione reduction, impaired calcium metabolism, and alteration of cytochrome P-450 activity; (3) blockade of iron chelators because of structural similarities to them or their precursors; (4) mediation of the production of endogenous dopaminergic neurotoxins, such as trichloroharmanes or isoquinolines; (5) blockade of dopamine receptors because of their resemblance to chemicals with affinity to these receptors; (6) stimulation of prostaglandin-H synthase and monooxygenase activity; and (7) stimulation of autoimmune processes and creation of autoimmunity to structures of the dopaminergic system caused by chemical similarity. (C) 1997 Academic Press.

Kuriwaka R, Mitsui T, Fujiwara S, Nishida Y, Matsumoto T. 2002. Loss of postural reflexes in long-term occupational solvent exposure. Eur Neurol 47(2): 85-87.
Abstract: Inhalation of organic solvents has long been known to damage various nervous systems, including cerebellum, brainstem, and pyramidal tract. However, little is known about the damage of the dopaminergic system. We report two patients with occupational long-term solvent exposure who developed postural instability without other features of parkinsonism. The concentration of HVA in CSF was decreased and the retropulsion was dramatically improved after the administration of levodopa. These findings indicate that the nigrostriatal dopaminergic neurons were disturbed by chronic solvent exposure, resulting in the loss of postural reflexes. Copyright (C) 2002 S. Karger AG, Basel.

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.

Laxmikanthan G, Blaber SI, Bernett MJ, Scarisbrick IA, Juliano MA, Blaber M. 2005. 1.70 angstrom X-ray structure of human apo kallikrein 1: Structural changes upon peptide inhibitor/substrate binding. Proteins-Structure Function and Bioinformatics 58(4):802-814.
Abstract: Human kallikreins are serine proteases that comprise a recently identified large and closely related 15-member family. The kallikreins include both regulatory- and degradative-type proteases, impacting a variety of physiological processes including regulation of blood pressure,

neuronal health, and the inflammatory response. While the function of the majority of the kallikreins remains to be elucidated, two members are useful biomarkers for prostate cancer and several others are potentially useful biomarkers for breast cancer, Alzheimer's, and Parkinson's disease. Human tissue kallikrein (human K1) is the best functionally characterized member of this family, and is known to play an important role in blood pressure regulation. As part of this function, human K1 exhibits unique dual-substrate specificity in hydrolyzing low molecular weight kininogen between both Arg-Ser and Met-Lys sequences. We report the X-ray crystal structure of mature, active recombinant human apo K1 at 1.70 Angstrom resolution. The active site exhibits structural features intermediate between that of apo and pro forms of known kallikrein structures. The S2 to S2' pockets demonstrate a variety of conformational changes in comparison to the porcine homolog of K1 in complex with peptide inhibitors, including the displacement of an extensive solvent network. These results indicate that the binding of a peptide substrate contributes to a structural rearrangement of the active-site Ser 195 resulting in a catalytically competent juxtaposition with the active-site His 57. The solvent networks within the S1 and S1' pockets suggest how the Arg-Ser and Met-Lys dual substrate specificity of human K1 is accommodated. Proteins (C) 2005 Wiley-Liss, Inc.

Lee DW, Opanashuk LA. 2004. Polychlorinated biphenyl mixture aroclor 1254-induced oxidative stress plays a role in dopaminergic cell injury. Neurotoxicology 25(6):925-939.
Abstract: Oxidative stress (OS) is thought to participate in the pathogenesis of neurodegenerative disorders, including Parkinson's disease (PD). Excessive reactive oxygen species (ROS) production can occur during the normal aging process or following exposure to environmental toxicants. Dopamine neurons, which degenerate during PD, are particularly sensitive to oxidative stress. Polychlorinated biphenyls (PCBs), persistent and widespread pollutants, have been shown to adversely impact dopaminergic (DAergic) pathways, but the role ROS play in neurotoxicity remains unclear To test the hypothesis that PCB exposure compromises dopamine neurons by stimulating ROS production, the direct toxicity and oxidative stress response following PCB exposure was examined both in MN9D dopamine cells and primary mesencephalic cultures. PCBs induced a time- and concentration-dependent increase in ROS production, which preceded cytotoxicity. Whereas intracellular GSH depletion exacerbated PCB effects, antioxidant pretreatment attenuated ROS production and cell death. Coincident alterations in antioxidant defense enzymes also accompanied ROS production, including decreased MnSOD and increased CuZnSOD protein levels. The robust elevation in heme oxygenase-1 levels further support the activation of oxidative stress mechanisms following PCB exposure. Furthermore, PCBs produced concentration-dependent reductions in intracellular dopamine levels and elevated dopamine turnover. Although the intracellular source of ROS remains unknown, these results suggest that sublethal PCB concentrations activate an oxidative stress-related pathway, which potentially disrupts dopamine neuron function. (C) 2004 Elsevier Inc. All rights reserved.

Lee JY, Kim JW, Lim HS, Joo WH, Cho YK, Moon JY. 2005. Changes in antioxidant defense systems by 2,2 ',5,5 '-tetrachlorobiphenyl exposure in neuronal SK-N-MC cells. Toxicol Lett 157(2):139-149.
Abstract: Polychlorinated biphenyls (PCBs) are known to alter the mammalian antioxidant defense system. To determine whether similar detoxification processes are activated in human neuronal cells, we investigated activities of antioxidant enzymes and the glutathione status (i.e., the levels of reduced and oxidized glutathione, GSH and GSSG) in human neuronal SK-N-MC cells exposed to 2,2',5,5'-tetrachlorobiphenyl (PCB 52). Upon PCB 52 treatment, time- and concentration-dependent inhibitions of cell viability were observed. PCB 52 did not affect GSH contents upon increasing the concentration up to 15 mu g/ml, but significant depletions in GSH were observed at the concentrations of 20 and 25 mu g/ml. PCB 52 exposure increased GSSG levels in the SK-N-MC

cells, while GSH levels were decreased, and these changes naturally modified the GSSG/GSH ratios. Cytosolic glutathione S-transferase (GST) activity with 1-chloro-2,4-dinitrobenzene as substrate was enhanced by two-fold in neuronal cells after exposure to PCB 52 versus controls. In contrast, neuronal cells showed a sustained decrease in glutathione peroxidase activity with increasing concentrations of PCB 52, and a sustained decrease in Cu/Zn-superoxide diSMLItase (SOD) activity with increasing concentrations of PCB 52. Catalase activity was increased until 12 h after exposure to PCB 52, but was decreased 24 It after exposure. Overall, these results imply a major effect of PCB 52 on GSH status and upon the activities of antioxidant enzymes in human neuronal SK-N-MC cells, and upon the overall process of detoxification in human neuronal cells. (c) 2005 Elsevier Ireland Ltd. All rights reserved.

Livertoux MH, Lagrange P, Minn A. 1996. The superoxide production mediated by the redox cycling of xenobiotics in rat brain microsomes is dependent on their reduction potential. Brain Res 725(2):207-216.
Abstract: Several exogenous molecules undergo enzymatic one-electron reduction leading to radicals which can rapidly react with molecular oxygen to form superoxide anions. We have previously shown that under aerobic conditions a significant superoxide anion production occurred during the NADPH-dependent one-electron reduction of some drugs and xenobiotics by rat brain preparations. We report here for several compounds a fairly good correlation between the reduction potentials (Epc vs. SCE) which ranged between - 230 and - 700 mV in aqueous medium (pH 7.4) or between - 700 mV and - 1100 mV in the aprotic solvent N,N-dimethylformamide, and the rate of superoxide anion production during their metabolism by rat brain microsomes. The data obtained suggest that the redox potential of most of the molecules assayed was related to their ability to undergo one-electron reduction mediated by flavoenzymes in the rat brain. The main range of reduction potentials corresponding to a large superoxide anion production suggests that the redox cycling of these chemicals was mediated by NADPH-cytochrome P-450 reductase. Therefore the measurement of reduction potentials of drugs and xenobiotics able to reach the brain, and chemically related to quinones, nitroaromatics, nitroheterocyclics and iminiums, may provide information both on their electron affinity and the possibility of one-electron transfer in vivo, and thus on their possible neurotoxicity due to the production of oxygenated free radicals.

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.

Louis ED, Applegate LM, Factor-Litvak P, Parides MK, Andrews L. 2004. Essential tremor - Occupational exposures to manganese and organic solvents. Neurology 63(11):2162-2164.
Abstract: Occupational exposures to manganese and organic solvents cause parkinsonism as well as prominent action tremor, resembling essential tremor (ET), yet their association with ET has not been studied. These chemicals cause cerebellar pathology. Cerebellar changes have been linked with ET. Using lifetime occupational histories, the authors demonstrated that occupational exposures were similar in cases and controls, which does not support an etiologic link between occupational

exposures to these chemicals and ET.

Lucarelli C, Betto P, Ricciarello G, Giambenedetti M, Corradini C, Stocchi F, Belliardo F. 1990 Jul 6. Simultaneous measurement of L-dopa, its metabolites and carbidopa in plasma of parkinsonian patients by improved sample pretreatment and high-performance liquid chromatographic determination. J Chromatogr 511:167-76.
Abstract: A procedure is described for the determination of L-3,4-dihydroxyphenylalanine (L-DOPA), its metabolites and carbidopa (CD) in plasma of Parkinsonian patients by high-performance liquid chromatography with dual working-electrode coulometric electrochemical detection. An efficient sample preparation scheme is presented for the isolation of L-DOPA, its metabolites and the catecholamines from the same plasma aliquot. After a simple deproteinization with methanol containing 2% of 0.5 M perchloric acid and evaporation of the solvent, L-DOPA, its metabolites and CD were separated with a 5-micron Nucleosil C18 column. Catecholamines were extracted from the supernatant of the deproteinized plasma by ion exchange on small columns and adsorption on alumina. Recoveries were close to 100% for L-DOPA, its metabolites and CD and 70% for catecholamines. The use of the same mobile phase for the concurrent assay of L-DOPA, its metabolites and catecholamines considerably increased the throughput of samples in the chromatographic system. The dual-electrode coulometric detector afforded peak identification by comparing current ratios. Monitoring of data from patients under L-DOPA therapy is reported.

Magnus NA, Aikins JA, Cronin JS, Diseroad WD, Hargis AD, Letourneau ME, Parker BE, Reutzel-Edens SM, Schafer JP, Staszak MA, Stephenson GA, Tameze SL, Zollars LMH. 2005. Diastereomeric salt resolution based synthesis of LY503430, an AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) potentiator. Organic Process Research & Development 9(5):621-628.
Abstract: This article describes the development and optimization of chemical reactions and subsequent preparation of the API LY503430 under cGMPs to fund first human dose (FHD) clinical evaluation as a potential therapeutic agent for Parkinson's disease. Reasons and rationale are presented for changes in solvents and reagents. One of the major developments presented here is the replacement of a chiral chromatography with a diastereomeric salt resolution. This article also discusses a preferred orientation issue with LY503430 which complicated the XRPD analysis.

Mariussen E, Fonnum F. 2003. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. Neurochem Int 43(4-5):533-542.
Abstract: The environmental levels of brominated flame retardants (BFRs) are increasing, but little is known about their toxic effects. In this paper, we show that some of the most important BFRs in commercial use today, have a neurotoxicological potential. Hexabromocyclododecane (HBCD) and tetrabromobisphenol-A (TBBPA) inhibit plasma membrane uptake of the neurotransmitters dopamine, glutamate and gamma-amino-n-butyric acid (GABA) at a concentration level similar to what previously found for polychlorinated biphenyls (PCBS) and even for ecstasy. The IC50 value for HBCD on dopamine uptake was 4 muM, and the IC50 values for TBBPA were 9, 6 and 16 muM for dopamine, glutamate and GABA, respectively. HBCD also inhibited glutamate uptake at low concentrations, but never achieved more than 50% inhibition. The inhibition was primarily due to their effect on the membrane potential, measured by the membrane potential marker tetrapherylphosphonium. bromide (TPP+). Other brominated flame retardants such as octaBDE and decaBDE did not have any effects on uptake. TBBPA, HBCD and even the pentabrominated diphenylether mixture (pentaBDE, DE-71, Great Lakes) also inhibited the vesicular uptake of dopamine with an IC50 value of 3, 3 and 8 muM, respectively. The neurotoxicological consequences of these findings for environmental contaminants such as BFRs and PCBs are discussed. (C)

Maruyama W. 2001 Jul. [Pathogenesis of idiopathic Parkinson's disease]. Nippon Ronen Igakkai Zasshi 38(4):494-7.
Abstract: The pathogenesis of idiopathic Parkinson's disease (PD) remains to be elucidated. The discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) suggests that neurotoxins in the human brain may cause selective depletion of striatal dopamine neurons, a hallmark of PD. An endogenous isoquinoline, N-methyl(R)salsolinol is a most promising neurotoxin candidate, and it was proved to be selectively toxic to dopamine neurons in the rat brain by in vivo experiments. The level of N-methyl(R)salsolinol in the cerebrospinal fluid obtained from PD patients was significantly higher than control. N-Methyl(R)salsolinol is synthesized by 2 enzymatic reactions from dopamine; condensation of dopamine with acetaldehyde into (R)salsolinol by (R)salsolinol synthase and N-methylation of (R)salsolinol by neutral(R)salsolinol N-methyltransferase. The second enzyme, which catabolizes the N-methylation of (R)salsolinol, was found to determine the level of the neurotoxin in the brain. The activity of neutral (R)salsolinol N-methyltransferase was examined using lymphocytes prepared from PD patients, normal controls and diseased controls as enzyme source. A significant increase in the activity was confirmed in lymphocytes from PD cases compared to normal- and diseased-control. Studies to clarify the environmental and genetic factors determining the activity of the enzyme are now under the way. The cytotoxicity of N-methyl (R)salsolinol was examined using a cultured cell model. N-Methyl(R) salsolinol was found to induce apoptotic cell death in a dose-dependent way. The mechanism of apoptosis was clarified to be mediated by collapse in mitochondrial membrane potential, activation of caspase 3 and fragmentation of nuclear DNA. In addition, propargylamines protected the cells from apoptosis. It was suggested that N-methyl(R)salsolinol and propargylamines have specific binding sites in mitochondria which regulate the death signal transduction. Propargylamines might be applicable as neuroprotective drugs, which can be orally administrated to PD patients.

Maruyama W, Narabayashi H, Dostert P, Naoi M . 1996. Stereospecific occurrence of a parkinsonism-inducing catechol isoquinoline, N-methyl(R)salsolinol, in the human intraventricular fluid. J Neural Transm 103(8-9):1069-1076.
Abstract: N-Methyl(R)salsolinol, an endogenous neurotoxin, has been proposed to be closely involved in the pathogenesis of Parkinson's disease. The selective toxicity to dopaminergic neurons was strictly limited for (R) enantiomer of N-methylsalsolinol. Its precursor, (R)salsolinol was enzymatically synthesized from dopamine and acetaldehyde in human. However, it has never been examined whether a non-enzymatic reaction produces racemic salsolinol derivatives from dopamine especially in patients under L-DOPA therapy. To clarify the point, their contents were examined in intraventricular fluid from parkinsonian patients administrated with L-DOPA. Only (R)enantiomer of N-methylsalsolinol and very low concentration of salsolinol could be detected. The results suggest that N-methyl(R)salsolinol synthesis may not depend on dopamine level, but on the activity of enzymes related to its synthesis and/or catabolism. The results are discussed in relation to pathogenesis Parkinson's disease.

Matsubara K. 1998 Oct. [Metabolic activation of azaheterocyclics induced dopaminergic toxicity: possible candidate neurotoxins underlying idiopathic Parkinson's disease]. Nippon Hoigaku Zasshi 52(5):301-5.
Abstract: In 1983, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant of "synthetic heroin", has been reported to induce parkinsonian symptoms in humans, who were responsive to L-DOPA therapy, as a result of the degeneration of nigrostriatal neurons. The "MPTP story" hypothesizes that Parkinson's disease may be initiated or percipitated by environmental and/or endogenous toxins by a mechanism similar to that of MPTP in genetically-predisposed individuals. Several classes of heterocyclic molecules structurally related to MPTP have been advanced as possible neurotoxicant precursors underlying the nigrostriatal degeneration in Parkinson's disease. Indoleamine-related beta-carbolines

(beta Cs), a class of heterocyclics which are basically plant alkaloids, are proposed as the most promising natural MPTP-like toxicants or protoxicants. In this article, beta Cs and N-methylated beta C cations are reviewed with regards to their formation, bioactivation, toxicity and presence in the human central nervous system. The enzymes in mammalian brain particulate fractions methylate beta Cs, sequentially forming 2-mono-[N]-methylated (2-Me beta C+s) and neurotoxic 2,9-di-[N, N']-methylated (2,9-Me2 beta C+s) beta-carbolinium cations. These beta C +s are structural analogs of 1-methyl-4-phenylpyridinium ion (MPP+), an active metabolite of MPTP, with a nitrogen bridge. The beta C+s not only inhibit DA reuptake and tyrosine hydroxylase, but also function as NADH-linked respiratory inhibitors in isolated mitochondria. The quarternization of beta C strikingly increased the affinity for dopamine transporter with 2-10 times greater Km and 10 times smaller Vmax values than MPP+. Furthermore, we have found higher concentrations of beta C+s localized in the nigra than in the cortex, and observed the S-adenosyl-L-methionine-dependent methylation of 2[beta]- and 9[indole]-nitrogens of beta Cs in non-parkinsonian human brains. Moreover, the cerebrospinal fluid levels of these beta C+s are higher in parkinsonian than non-parkinsonian patients. Simple beta-carboline induced parkinsonian-like symptoms in mice via N-methylation. These results indicated that beta C is a selective dopaminergic toxin precursor, that is sequentially methylated to form 2,9-Me2 beta C+ that could be an underlying factor in idiopathic Parkinson's disease.

Matsubara K, Ota M, Takahashi T, Maruyama W, Naoi M. 1994. Structural studies of condensation products of biogenic-amines as inhibitors of tryptophan-hydroxylase. Brain Res 655(1-2):121-127.
Abstract: The effects of condensation products of dopamine and indoleamines on the activity of tryptophan hydroxylase (TPH) were evaluated to determine the structures associated with modulation of this enzyme activity. The compounds having a catechol structure, such as 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, markedly inhibited the activity of the enzyme prepared from the rat brain. The inhibition was non-competitive in terms of both the biopterin cofactor and the substrate L-tryptophan. Substitution on the one or two positions of catechol isoquinolines did not affect the inhibitory activity towards TPH. Among these compounds, a charged substance, 1,2[N]-dimethyl-6,7-dihydroxy-isoquinolinium ion, as an extremely potent inhibitor; the K-i values were 0.88 +/- 0.17 and 0.64 +/- 0.08 mu M (mean +/- S.D.) in terms of the substrate and cofactor, respectively. By contrast, the condensation products of tryptophan and tryptamine with acetaldehyde scarcely affected TPH activities. 1-Methyl-1,2,3,4-tetrahydroisoquinoline, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 1-methyl-4-phenylpyridinium ion (MPP(+)) were almost inactive. These results indicated that the catechol structure recognized and combined with TPH at a binding site different from that of the substrate or cofactor and the positive charge on the dopamine-derived substance enhanced the affinity to TPH. The selective inhibition of TPH by dopamine-derived catechol isoquinolines were discussed in relationship to the interactions between catecholamines, indoleamines and their metabolites in the brain under physiological and pathological conditions.

Mayor-Rios J, Del Castillo-Martin N, Lopez-Hernandez V, Galan-Garcia L, Suarez-Murias C, Charro-Ruiz L. 2003. Selective attention disorders associated with a history of occupational exposure to organic solvents. Rev Neurol 37 (11):1013-1021.
Abstract: Introduction. The cognitive effects of long-term exposure to organic solvents could be similar to those triggered by certain neurodegenerative diseases. Aims. The purpose of this study was to evaluate the effects exerted by accumulated exposure on the cognitive functions. Patients and methods. 105 subjects with an average history of exposure of 19.3 years were evaluated using seven computerised cognitive tasks (CPT, digit-symbol substitution, Stroop, memory span, word learning and recognition, and TRD) and results were later compared with the performance of a non-exposure group and with a normative reference.

A study was made of the association between the length of exposure and performance in the variables in which the exposed subjects displayed significantly lower values than control subjects. In order to evaluate the effect exerted by age, regression functions between performance and age were calculated for each group. Results. Only the indicators from the Stroop and digit-symbol tasks correlated with the length of exposure. The regression functions between performance and age for each group showed that the former decreased significantly faster among exposed subjects than among controls. Conclusions. Findings suggest that, while recent exposure seems to have an effect on a wide range of functions, chronic exposure exerts a selective influence on a smaller group. In this case, only selective attention appears to deteriorate. Similar deficits have been observed in the early stages of patients with Alzheimer and Parkinson.

Mcdonnell L, Maginnis C, Lewis S, Pickering N, Antoniak M, Hubbard R, Lawson I, Britton J. 2003. Occupational exposure to solvents and metals and Parkinson's disease. Neurology 61(5):716-717.

Melamed E, Friedberg G, Zoldan J. 1999. Psychosis - Impact on the patient and family. Neurology 52(7):S14-S16.
Abstract: Psychosis represents a milestone in the progression of PD, often severely taxing caregivers and frequently warranting nursing-home placement. This step is often necessary because caregivers cannot tolerate, among other stressors, their loved ones' sexual aberrations and irrational accusations (which can be caused by paranoid ideation). Other salient features of parkinsonian psychosis comprise vivid nightmares, which often herald its onset; hallucinations, which are principally visual and stereotypical in content; agitation; aggression; delirium; and confusion that exceeds the typical erosion in mentation. Hallucinosis and paranoid ideation may in turn precipitate weight loss; food may be deemed inedible because of imagined contaminants, for instance, either worm infestations or a delusional fear of poisoning by the caregiver. Parkinsonian psychosis exhibits an age predilection; correlates with the duration of disease and levodopa therapy; and may be associated with increases in the dosage of this agent or other drugs given, either as monotherapy or with levodopa. Levodopa or dopamine agonist toxicity can lead to psychosis because of dopaminergic hypersensitivity. Unfortunately, attempts to diminish this untoward effect (eg, reducing the levodopa dosage, introducing neuroleptics) may curb the psychosis but also erode control of parkinsonian features. To avert this "dopamine dilemma," we have tested a selective serotonin antagonist (ondansetron), which essentially attenuated visual hallucinosis, improved delusional ideation and confusion, and was well tolerated. Other agents that can be tried for parkinsonian psychosis include the atypical neuroleptics olanzapine and clozapine.

Melzig MF, Zipper J. 1993. Effects of salsolinol on cultivated endothelial-cells. Neurochem Res 18(6):689-693.
Abstract: In view of neurotoxic properties of tetrahydroisoquinolines (TIQ's) there are open questions also in regard to the disturbance of the blood-brain barrier. Because endothelial cells are an important element of this barrier the present study was designed to assess the influence of salsolinol (a TIQ formed by condensation of dopamine and acetaldehyde) on cultivated endothelial cells by physiological, biochemical and morphological investigations. For the investigations we used aortic endothelial ce!ls because of a variety of similarities in physiology and biochemistry to brain capillary endothelial cells. Cytotoxic effects estimated by cell counting after 72 h treatment with salsolinol (IC50 = 38 mumol/1) were possibly caused by mitochondrial damages. Already after 2 h severe ultrastructural alterations of many mitochondria could be observed. The respiration activity of the cells was always inhibited after treatment with salsolinol for some hours. The damage of the mitochondria by salsolinol was not connected with inhibition of the activity of succinate dehydrogenase and cytochrome c + c1. Nevertheless the damages of mitochondrial integrity support the hypothesis that the neurotoxic effect of salsolinol is primarily caused by damaging the endothelial cells associated

with a disturbance of blood-brain barrier.

Miller DW, Wilson CR, Kaleem MA, Blackinton J, Cookson MR. 2005. Identification of the epitope of a monoclonal antibody to DJ-1. Neurosci Lett 374(3): 203-206.
Abstract: Mutations in DJ-1 can cause early onset parkinsonism. Various antibodies have been generated to detect this protein, one of which is a commonly used monoclonal antibody (clone 3E8). Since results of in situ examinations of DJ-1 expression with this antibody have differed from analyses with species-specific antibodies (e.g. rat), it would be useful to know the epitope for this antibody. Using GFP-tagged deletion constructs of human DJ-1, we have localized the epitope region for this antibody to within residues 56-78 of human DJ-1. Mapping this region to the published three-dimensional structure of DJ-1 indicates that this is a solvent-accessible surface epitope. Immunonegativity of E64D mutant DJ-1 with the monoclonal antibody suggests that glutamate 64 of human DJ-1 contributes to the epitope recognized by this antibody. Moreover, the loss of immunoreactivity due to such a small substitution demonstrates the remarkable sensitivity of the monoclonal antibody 3E8 to DJ-1. Published by Elsevier Ireland Ltd.

Morel P, Fauconneau B, Page G, Mirbeau T, Huguet F. 1998. Inhibitory effects of ascorbic acid on dopamine uptake by rat striatal synaptosomes: relationship to lipid peroxidation and oxidation of protein sulfhydryl groups. Neurosci Res 32(2):171-179.
Abstract: Ascorbic acid is frequently added in the incubation medium to prevent oxidation of dopamine (DA) during uptake assays. However, a preliminary study showed that the presence of ascorbic acid induced a decrease of DA uptake after prolonged incubation. The purpose of this study was to determine the mechanism underlying ascorbic acid-induced alterations of DA uptake in rat striatal synaptosomes. In this context, the effects of physiological concentrations of ascorbic acid (100-500 mu M) on DA uptake and Na+/K+ ATPase activity (which is essential for DA transporter function) were assessed in synaptosomes before and after incubation at 37 degrees C. The capacity of synaptosomes to take up DA was significantly decreased after incubation owing to a reduction in DA transporters (but with no modification of their affinity for DA). This partial inhibition was associated with a decrease of Na+/K+ ATPase activity, a production of thiobarbituric acid reactive substances (TBARS) and malonaldehyde (MDA), and a loss of sulfhydryl group content. Addition of Trolox C to the medium prevented the reduction of DA uptake, the inhibition of Na+/K+ ATPase activity, the decrease in sulfhydryl group content and the production of TEARS and MDA. These results suggest that ascorbic acid in the presence of contaminant ferrous ions induced a decrease in functional DA transporters, probably through a lipid peroxidation process involving oxidation of sulfhydryl groups and at least in part through a decrease of Na+/K+ ATPase activity. (C) 1998 Elsevier Science Ireland Ltd. All rights reserved.

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.

Mu M, Kung MP, Plossl K, Acton PD, Mozley PD, Kung HF. 1999. A simplified

method to determine [Tc-99m]TRODAT-1 in human plasma. Nucl Med Biol 26(7):821-825.
Abstract: [Tc-99m]TRODAT-1 is a useful imaging agent in evaluating changes in presynaptic dopamine transporters (DAT) for Parkinson's disease and other central nervous system (CNS) neurodegenerative diseases, for which a reduction of dopamine neurons is indicated. As part of an effort to establish a quantitative single photon emission tomography (SPECT) procedure for imaging CNS DAT, measurement of nonmetabolized [Tc-99m]TRODAT-1 in human plasma was investigated. After an intravenous injection of [Tc-99m]TRODAT-1, there are three possible radioactive components in human plasma: hydrophilic compounds (pertechnetate, etc.), lipophilic metabolite(s), and unchanged [Tc-99m] TRODAT-1. Based on the differences in lipophilicity of [Tc-99m]TRODAT-1 and its lipophilic metabolite [Tc-99m]BAT, a new quantitative method for measuring [Tc-99m]TRODAT-1 with a simple solvent extraction method was developed. Various organic solvents or mixtures of solvents were tested, among which cyclohexane gave the best extraction yield for [Tc-99m]TRODAT-1 (76.06 +/- 3.32%) with a low extraction for [Tc-99m] BAT (2.43 +/- 0.82%). Extractions of [Tc-99m]TRODAT-1 and [Tc-99m] BAT mixtures in different predetermined ratios to simulate the actual human plasma samples with cyclohexane from phosphate buffer (5 mM, pH 8.0) were evaluated. The experimentally obtained ratios were in good agreement with the theoretical ratios. To investigate further the possibility of replacing the previously established high performance liquid chromatography (HPLC) method with the new solvent extraction method for the clinical application, both HPLC and extraction methods were used side by side to determine the unchanged [Tc-99m]TRODAT-1 in human plasma samples during [Tc-99m]TRODAT-1/SPECT imaging studies. The results from four human subjects showed that both methods consistently produced similar values for unchanged [Tc-99m]TRODAT-1 in the plasma samples. This improved solvent extraction method provides an easy and reliable technique to quantify unchanged [Tc-99m]TRODAT-1 in human plasma, thus making the clinical application of this agent readily available for quantitation of the DAT binding sites in the brain by SPECT imaging. NUCL MED BIOL 26;7: 821-825, 1999. (C) 1999 Elsevier Science Inc. All rights reserved.

Munishkina LA, Phelan C, Uversky VN, Fink AL . 2003. Conformational behavior and aggregation of alpha-synuclein in organic solvents: Modeling the effects of membranes. Biochemistry (Mosc) 42(9):2720-2730.
Abstract: Intracellular proteinaceous inclusions (Lewy bodies and Lewy neurites) of alpha-synuclein are pathological hallmarks of neurodegenerative diseases Such as Parkinson's disease, dementia with Lewy bodies (DLB), and multiple systemic atrophy. The molecular mechanisms underlying the aggregation of alpha-synuclein into such filamentous inclusions remain unknown, although many factors have been implicated, including interactions with lipid membranes. To model the effects of membrane fields on alpha-synuclein, we analyzed the structural and fibrillation properties of this protein in mixtures of water with simple and fluorinated alcohols. All solvents that were studied induced folding of alpha-synuclein, with the common first stage being formation of a partially folded intermediate with an enhanced propensity to fibrillate. Protein fibrillation was completely inhibited due to formation of beta-structure-enriched oligomers with high concentrations of methanol, ethanol, and propanol and moderate concentrations of trifluoroethanol (TFE), or because of the appearance of a highly alpha-helical conformation at high TFE and hexafluoro-2-propanol concentrations. At least to some extent, these conformational effects mimic those observed in the presence of phospholipid vesicles, and can explain some of the observed effects of membranes on alpha-synuclein fibrillation.

Murray IVJ, Giasson BI, Quinn SM, Koppaka V, Axelsen PH, Ischiropoulos H, Trojanowski JQ, Lee VMY. 2003. Role of alpha-synuclein carboxy-terminus on fibril formation in vitro. Biochemistry (Mosc) 42(28):8530-8540.
Abstract: Alpha-synuclein (alpha-syn) is the major component of

intracellular inclusions in several neurodegenerative diseases, and the conversion of soluble alpha-syn into filamentous aggregates may contribute to disease pathogenesis. Since mechanisms leading to the formation of alpha-syn inclusions are unclear, in vitro models of alpha-syn aggregation may yield insights into this process. To that end, we examined the consequences on the progressive deletion of the carboxy-terminus of alpha-syn in regulating fibril formation, and we show here that carboxy-terminal truncated alpha-syn proteins aggregate faster than the full-length molecule. Protease digestion and immunoelectron microscopy indicate that the alpha-syn amino- and carboxy-termini are more solvent exposed than the central core and that filaments formed from carboxy-terminal truncated alpha-syn are narrower in diameter than the full-length molecule. Moreover, seeding experiments under conditions where full-length alpha-syn did not readily aggregate revealed that carboxy-truncated alpha-syn extending from amino acids 1-102 and 1-110 but not 1-120 were efficient in seeding full-length alpha-syn aggregation over a range of concentrations. Using site-directed mutagenesis, the negatively charged residues 104, 105 and 114, 115 in the carboxy-terminus were implicated in this reduced aggregation and the lack of seeding of full-length alpha-syn fibrillogenesis by 1-120. Our data support the view that the middle region of alpha-syn forms the core of alpha-syn filaments and that negative charges in the carboxy-terminus counteract alpha-syn aggregation. Thus, the carboxy-terminus of alpha-syn may regulate aggregation of full-length alpha-syn and determine the diameter of alpha-syn filaments.

Naoi M, Maruyama W, Dostert P, Hashizume Y. 1996. Animal model of Parkinson's disease induced by naturally-occurring 1(R),2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline. Biogenic Amines 12(2):135-147. Abstract: A dopamine-derived isoquinoline, 1(R), 2-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, 2(N)-methyl-(R)-salsolinol [NM (R)Sal], could induce parkinsonism into rats. After injection into the striatum, NM(R)Sal and its oxidation product, 1,2-dimethyl-6,7-dihydroxyisoquinolinium ion (DMDHIQ(+)) caused behavioral changes very similar to Parkinson's disease. Biochemical analysis revealed the reduction of dopamine and noradrenaline in the substantia nigra in addition to the striatum, accompanied with DMDHIQ(+) accumulation. The density of dopamine neurons stained with anti-tyrosine hydroxylase antibody was reduced in the substantia nigra after one week of continuous infusion of NM (R)Sal in the striatum. In addition, only R-enantiomers of Sal and NMSal were identified in the human brain, and an enzyme was isolated, which catalyzes the condensation of dopamine or N-methyldopamine with acetaldehyde to produce the R-enantiomers of Sal or NMSal. The possible involvement of NM(R)Sal in the pathogenesis of Parkinson's disease is discussed.

Naoi M, Maruyama W, Dostert P, Kohda K, Kaiya T. 1996. A novel enzyme enantio-selectively synthesizes (R)salsolinol, a precursor of a dopaminergic neurotoxin, N-methyl(R)salsolinol. Neurosci Lett 212(3):183-186. Abstract: In the human brain, only (R)enantiomer of 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline ((R)salsolinol) and N-methylsalsolinol, a dopaminergic neurotoxin, were detected, suggesting their enzymatic biosynthesis. This paper reports the isolation and characterization of a novel enzyme, which enantio-selectively synthesizes (R)salsolinol from dopamine and acetaldehyde. Dopamine, acetaldehyde, formaldehyde and pyruvic acid were the substrates of this synthase, whereas N-methyldopamine, adrenaline, noradrenaline and L-DOPA were not. The possible function of this enzyme under physiological and pathological conditions in the brain is discussed.

Naoi M, Maruyama W, Nagy GM. 2004. Dopamine-derived salsolinol derivatives as endogenous monoamine oxidase inhibitors: Occurrence, metabolism and function in human brains. Neurotoxicology 25(1-2):193-204. Abstract: Salsolinol, 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, is an endogenous catechol isoquinoline detected in humans by M. Sandler In human brain, a series of catechol isoquinolines

were identified as the condensation products of dopamine or other monoamines with aldehydes or keto-acids. Recently selective occurrence of the (R)enantiomers of salsolinol derivatives was confirmed in human brain, and they are synthesized by enzymes in situ, but not by the nonenzymatic Pictet-Spengler reaction. A (R)salsolinol synthase catalyzes the enantio-specific synthesis of (R)salsolinol front dopamine and acetaldehyde, and (R)salsolinol N-methyltransferase synthesizes N-methyl (R)salsolinol, which is further oxidized into 1,2-dimethyl-6,7-dihydroxyisoquinolinium ion by non-enzymatic and enzymatic oxidation. The stepwise reactions, N-methylation and oxidation, induce the specified distribution of the N-methylated and oxidized derivatives in the human nigro-striatum, suggesting that these derivatives may be involved in the function of dopamine neurons under physiological and pathological conditions. As shown by in vivo and in vitro experiments, salsolinol derivatives affect the levels of monoamine neurotransmitters though the inhibition of enzymes related in the metabolism of catechol- and indoleamines. In addition, the selective neurotoxicity of N-methyl(R) salsolinol to dopamine neurons was confirmed by preparation of an animal model of Parkinson's disease in rats. The involvement of N-methyl(R) salsolinol in the pathogenesis of Parkinson's disease was further indicated by the increase in the N-methyl(R)salsolinol levels in the cerebrospinal fluid and that in the activity of its synthesizing enzyme, a neural (R)salsolinol N-methyltransferase, in the lymphocytes prepared from parkinsonian patients. N-Methyl(R)salsolinol induces apoptosis in dopamine neurons, which is mediated by death signal transduction in mitochondria. In addition, salsolinol was found to function as a signal transmitter for the prolactin release in the neuro-intermediate lobe of the brain. These results are discussed in relation to role of dopamine-derived endogenous salsolinol derivatives as the regulators of neurotransmission, dopaminergic neurotoxins and neuro-hormonal transmitters in the human brain. (C) 2003 Elsevier Inc. All rights reserved.

Ngim CH, Devathasan G. 1989. Epidemiologic study on the association between body burden mercury level and idiopathic Parkinson's disease. Neuroepidemiology 8(3):128-41.
Abstract: A case-control study was conducted among the multiethnic population of Singapore to test the hypothesis that a high level of body burden mercury is associated with an increased risk of Parkinson's disease (PD). Selected factors investigated that could contribute to the body burden of mercury included dietary fish intake, ethnic over-the-counter medications, occupational exposures and possession of dental amalgam fillings. Detailed interviews were completed in 54 cases of idiopathic PD and 95 hospital-based controls, matched for age, sex and ethnicity, between July 1985 and July 1987. After adjusting for potential confounding factors, including dietary fish intake, medications, smoking and alcohol consumption, there was clear monotonic dose-response association between PD and blood mercury levels. The odds ratios (OR) and 95% confidence intervals (CI) for the approximate subject tertiles based upon blood mercury levels were 8.5 (CI = 2.2-33.2) and 9.4 (CI = 2.5-35.9), relative to the tertile with lowest blood mercury levels (less than 5.8 ng Hg/ml). Similar associations were revealed using scalp hair and urinary mercury levels. However, only the comparisons between the highest and lowest tertiles were statistically different from unity (p less than 0.05). When the body burden mercury indicators were mutually adjusted in addition to the four confounding factors, blood and urinary mercury levels showed ORs of 21.00 and 18.65, respectively. These ORs were statistically different from unity (p less than 0.05, 2-sided test). After adjustment, scalp hair mercury was shown to be a poor predictor of PD risk.

Nguon K, Ladd B, Baxter MG, Sajdel-Sulkowska EM. 2005. Sexual Dimorphism in Cerebellar Structure, Function, and Response to Environmental PerturbationsVolume 148. p 343-351. Creating Coordination in the Cerebellum: Progress in Brain Research.
Abstract: Sexual dimorphism of CNS structure and function has been observed in humans and animals, but remains relatively unrecognized in

the context of the cerebellum. Recent researh in our laboratory has examined whether these gender differences extend to cerebellar structure and function, as well as the impact of environmental factors on the developing cerebellum. Perinatal exposure to both chemical and physical perturbations in the environment (in our experiments, PCBs or hypergravity) affects growth, neurodevelopment, and motor coordination differently in males and females. These neurodevelopmental and behavioral effects are accompanied by sex-related changes in cerebellar mass and cerebellar protein expression. Exposure to chemical toxins (PCBs) resulted in more dramatic neurodevelopmental and behavioral changes in male neonates. It is possible that gender-related differences in male and female cerebellar structure and function are related to sex-specific development of the cerebellum and sex-specific distribution of specific receptors, local synthesis of trophic factors, and maturation of the pituitary hypophesial axis. These sex-related differences may underlie the sex-specific preponderance of certain neuropsychiatric disorders, and must be incorporated in the design of future basic and clinical investigations.

Normandin L, Panisset M, Zayed J. 2002 Jul-Sep. Manganese neurotoxicity: behavioral, pathological, and biochemical effects following various routes of exposure. Rev Environ Health 17(3):189-217.
Abstract: The human central nervous system is an important target for manganese intoxication, which causes neurological symptoms similar to those of Parkinson's disease. With the increasing use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an octane-improving additive to unleaded gasoline, the prospect of worldwide manganese exposure is once again attracting attention as increases in environmental manganese concentrations have been recorded relative to traffic density. One crucial question is whether a small increase of manganese contamination resulting from the widespread use of MMT could have neurotoxic effects. In this review we concentrate on central nervous system abnormalities and neurobehavioral disturbances. Most experimental animal studies on manganese neurotoxicity have been conducted in nonhuman primates and rodents. Most studies performed in rodents used oral manganese administration and did not assess bioaccumulation or central nervous system changes. The major effect found was transient modification of spontaneous motor activity. Very few inhalation toxicological studies were carried out. As manganese intoxication in humans usually occurs via inhalation, more studies are required using the respiratory route of administration. Given the proven neurotoxic effects of manganese and the prospect of worldwide MMT usage, this metal should be considered a new environmental pollutant having potentially widespread public health consequences.

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.

Ohlson CG, Hogstedt C. 1981. Parkinsons-disease and occupational exposure to organic-solvents, agricultural chemicals and mercury - a case-referent study. Scandinavian Journal of Work Environment & Health 7(4):252-256.

Ohya T, Niitsu M. 2005. Identification of 4-methylspinaceamine - a Pictet-Spengler condensation reaction product of histamine with acetaldehyde - in human urine. Life Sci 76(11):1199-1209.
Abstract: This study reports the first identification of 4-methylspinaceamine (4-MSPA)-a Pictet Spengler condensation reaction product of histamine with acetaldehyde-in human urine. 4-MSPA was identified and quantified as follows: the target compound was partially purified by solvent extraction from a urine sample spiked with N-methylpiperazine (N-MP) as an internal standard, then derivatized to a naphthylthiourea derivative with 1-naphthylisothiocyanate (NITC) and finally analyzed by HPLC. For verification, 4-MSPA was also analyzed by ion spray-mass spectrometry (IS-MS), using 4-MSPA-d(4) as an internal standard. The amount of 4-MSPA in human urine varied between individuals and from day-to-day, ranging from undetectable to 0.80 nmol/mL. (C) 2004 Elsevier Inc. All rights reserved.

Palfi S, Riche D, Brouillet E, Guyot MC, Mary V, Wahl F, Peschanski M, Stutzmann JM, Hantraye P. 1997 Jul. Riluzole reduces incidence of abnormal movements but not striatal cell death in a primate model of progressive striatal degeneration. Exp Neurol 146(1):135-41.
Abstract: Riluzole has been shown recently to increase life expectancy in patients with amyotrophic lateral sclerosis. A number of experimental studies also suggest that this compound may be a neuroprotectant. We have investigated in baboons whether riluzole would protect striatal neurons from a prolonged 3-nitropropionic acid (3NP) treatment and ameliorate the associated motor symptoms. In animals receiving 3NP and the solvent of riluzole, 12 weeks of high-dose 3NP treatment resulted in the appearance of persistent leg dystonia and significant increases in the incidence of three categories of abnormal movements and in the dyskinesia index in the apomorphine test (0.5 mg/kg i.m.). Quantitative assessment of these behavioral deficits using a video movement analysis system demonstrated a significant decrease in locomotor activity and peak tangential velocity in 3NP-treated animals compared to controls. Histological analysis showed the presence of severe, bilateral, striatal lesions, localized in both caudate and putamen. Cotreatment with riluzole (4 mg/kg i.p., twice daily) significantly reduced the dyskinesia index (-35%, $P < 0.02$) in the apomorphine test. In the quantitative behavioral analysis, riluzole significantly ameliorated the decrease in peak tangential velocity ($P < 0.02$) but not the decrease in locomotor activity observed after 3NP. Comparative histological analysis of the two groups of treated animals did not demonstrate a clear neuroprotective effect of riluzole. The present study suggests that one potential therapeutic interest for riluzole in neurodegenerative disorders may reside in the reduction of motor symptoms associated with striatal lesions.

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.

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 M, Ross GW, Petrovitch H, White LR, Masaki KH, Nelson JS, Tanner CM, Curb JD, Blanchette PL, Abbott RD. 2005. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. Neurology 64(6): 1047-1051.
Abstract: Objective: To examine the relation between milk and calcium intake in midlife and the risk of Parkinson disease (PD). Methods: Findings are based on dietary intake observed from 1965 to 1968 in 7,504 men ages 45 to 68 in the Honolulu Heart Program. Men were followed for 30 years for incident PD. Results: In the course of follow-up, 128 developed PD (7.1/10,000 person-years). Age-adjusted incidence of PD increased with milk intake from 6.9/10,000 person-years in men who consumed no milk to 14.9/10,000 person-years in men who consumed > 16 oz/day ($p = 0.017$). After further adjustment for dietary and other factors, there was a 2.3-fold excess of PD (95% CI 1.3 to 4.1) in the highest intake group (> 16 oz/day) vs those who consumed no milk. The effect of milk consumption on PD was also independent of the intake of calcium. Calcium from dairy and nondairy sources had no apparent relation with the risk of PD. Conclusions: Findings suggest that milk intake is associated with an increased risk of Parkinson disease. Whether observed effects are mediated through nutrients other than calcium or through neurotoxic contaminants warrants further study.

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.

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.

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.

Pezzoli G, Antonini A, Barbieri S, Canesi M, Perbellini L, Zecchinelli A, Mariani CB,

Bonetti A, Leenders KL. 1995. N-hexane-induced parkinsonism - pathogenetic hypotheses. Mov Disord 10(3):279-282.
Abstract: n-Hexane, similar hydrocarbons, and derivatives are common environmental pollutants and by-products of lipid peroxidation, and they may have a nigrotoxic effect like that of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. This report describes our second case of parkinsonism in a subject exposed to n-hexane. Positron emission tomography studies demonstrated regional striatal abnormalities of the nigrostriatal dopaminergic system and of glucose metabolism that were different from those found in idiopathic Parkinson's disease.

Pezzoli G, Canesi M, Antonini A, Righini A, Perbellini L, Barichella M, Mariani CB, Tenconi F, Tesei S, Zecchinelli A, Leenders KL. 2000. Hydrocarbon exposure and Parkinson's disease. Neurology 55(5):667-673.
Abstract: Background: Single cases of parkinsonism have been associated with hydrocarbon solvents. Objective: To determine whether exposure to hydrocarbon solvents is related to PD. Methods: Cohort study of 990 patients with PD according to Core Assessment Program for Intracerebral Transplantations (CAPIT) criteria, selected from 1455 consecutive subjects presenting at a referral center; case-control study assessing Unified PD Rating Scale scores (motor score as primary endpoint) in all subjects with positive history of hydrocarbon solvent exposure (n = 188), matched for duration of disease and gender to 188 subjects selected from the remaining 802 with a negative history. Two subgroups in the case-control study included the following: 1) response to apomorphine (n = 26); 2) brain MRI (n = 15). PET imaging (n = 9) was compared with that of historic controls. Results: Exposed patients were younger (61.0 +/- 9.4 versus 64.7 +/- 9.4 years, p = 0.002), predominantly male (76.4% versus 45.2%, p = 0.0001), less educated (8.4 +/- 4.2 versus 10.1 +/- 4.4 years, p = 0.0001), and younger at onset of disease (55.2 +/- 9.8 versus 58.6 +/- 10 years, p = 0.014). Exposure to hydrocarbon solvents directly correlated;to disease severity (r = 0.311) and inversely correlated to latency period (r = -0.252). Nine blue-collar occupations accounted for 91.1% of exposures. Conclusions: Occupations involving the use of hydrocarbon solvents are a risk factor for earlier onset of symptoms of PD and more severe disease throughout its course. Hydrocarbon solvents may be involved in the etiopathogenesis of PD, which does not have a major genetic component.

Pezzoli G, Ricciardi S, Masotto C, Mariani CB, Carenzi A. 1990 Oct 29. n-hexane induces parkinsonism in rodents. Brain Res 531(1-2):355-7.
Abstract: A case of human parkinsonism, due to n-hexane exposure, was recently described. On the basis of this observation, we treated mice and rats with n-hexane and its principle toxic metabolite 2,5-hexanedione. The mice underwent a chronic treatment intraperitoneum, the rats were treated stereotaxically into the substantia nigra. At biochemical analysis of the striata, dopamine and homovanillic acid levels were significantly lower compared with control animals; norepinephrine, serotonin, 5-hydroxindolacetic acid levels were unchanged. The rats treated with 2,5-hexanedione showed an apomorphine-induced rotational behavior significantly higher compared to controls. Since n-hexane and its metabolites are environmental contaminants and by-products of endogenous metabolic pathways, we propose that they may play a role in inducing parkinsonism in humans.

Purdey M. 2004. Elevated levels of ferrimagnetic metals in foodchains supporting the Guam cluster of neurodegeneration: Do metal nucleated crystal contaminents evoke magnetic fields that initiate the progressive pathogenesis of neurodegeneration? Med Hypotheses 63(5):793-809.
Abstract: Elevated levels of aluminium (At), strontium (Sr), barium (Ba), iron (Fe), manganese (Mn) cations combined with deficiencies of magnesium (Mg)/calcium (Ca) - have been observed in the foodchains that traditionally support the Chamorro populations affected by high incidence clusters of Alzheimer (AD), Parkinson-like (PD), motor neurone diseases and multiple sclerosis on the island of Guam. Soils drawn from the cluster region demonstrated an excessive fivefold increase in 'magnetic

susceptibility' readings in relation to soils from disease free adjoining regions. A multifactorial aetiological hypothesis is proposed that pivots upon the combined exposure to high levels of natural/industrial sources of ferrimagnetic/ferroelectric compounds incorporating A[, Fe, Mn, Sr, Ba (e.g., via yam/seafood consumption or exposure to world war 2 (WW2) munitions) and to low levels of Mg/Ca in all S. Pacific locations where these clusters of neurodegenerative disease have simultaneously erupted. Once gut/blood brain barrier permeability is impaired, the increased uptake of At, Fe, Sr, Ba, or Mn into the Mg/Ca depleted brain Leads to rogue metal substitutions at the Mg/Ca vacated binding domains on various enzyme/ proteoglycan groups, causing a broad ranging disruption in Mg/Ca dependent systems - such as the glutamine synthetase which prevents the accumulation of neurotoxic glutamate. The rogue metals chelate sulphate, disrupting sulphated-proteoglycan mediated inhibition of crystal proliferation, as well as its regulation of the Fibroblast growth factor receptor complex which disturbs the molecular conformation of those receptors and their regulation of transphosphorylation between intracellular kinase domains; ultimately collapsing proteoglycan mediated cell-cell signalling pathways which maintain the growth and structural integrity of the neuronal networks. The depression of Mg/Ca dependent systems in conjunction with the progressive ferrimagnetisation of the CNS due to an overload of rogue ferroelectric/ferrimagnetic metal contaminants, enables 'seeding' of metal-protein crystalline arrays that can proliferate in the proteoglycan depleted brain. The resulting magnetic field emissions initiate a free radical mediated progressive pathogenesis of neurodegeneration. The coclustering of these various types of disease in select geographical pockets around the world suggests that all of these conditions share a common early life exposure to ferromagnetic metal nucleating agents in their multifactorial aetiology. Factors such as individual genetics, the species of metal involved, etc., dictate which specific class of disease will emerge as a delayed neurotoxic response to these environmental insults. (C) 2004 Elsevier Ltd. All rights reserved.

Radil T, Roth J, Ruzicka E, Tichy J, Wysocki CJ. 1995. Olfactory dysfunction: A symptom of Parkinson's disease? Ceska a Slovenska Neurologie a Neurochirurgie 58(6):286-289.
Abstract: To verify the concept of olfactory dysfunction of Parkinson's disease (PD), we studied olfactory functions in 16 patients with idiopathic PD and in 18 gender and age matched healthy controls. Amylacetate (banana smell) in 12 sequential dilutions (in 50% steps) was used as odorant in four conditions adopted in random order: (A) binary ascendent forced choice (odorant vs. pure solvent), (B) ascendent limit, and (C) descending limit thresholds, (D) time course od deadaptation after olfactory adaptation. The testing showed anosmia in one patient, six more patient and one control subject were found to be hyposmic. Average olfactory thresholds were slightly higher in the patients compared with healthy controls. The decrease of olfaction was unrelated to the age of the patients, duration of the disease, degree of motor impairment, dose and duration of L-DOPA treatment. The facilitatory effect of ascendent stimulus ordering (lower B than C threshold) representing a modulatory or adaptive phenomenon related to stimulus expectancy, was observed in the patients as well as in healthy controls. No difference in the time course of deadaptation was found between both groups. In conclusion, our study revealed olfactory disturbances in less than a half of the PD patients. The dysfunction was mostly limited to slight hyposmia, and no impairment of modulatory-adaptive olfactory phenomena was disclosed (lower (B) than (C) thresholds and no difference in (D) between both groups). Thus, olfactory impairment does not appear to he a pathognomonic symptom of PD and, if present, represents rather nonspecific sensory changes.

Ramsay RR, Mehlhorn RJ, Singer TP. 1989 Mar 31. Enhancement by tetraphenylboron of the interaction of the 1-methyl-4-phenylpyridinium ion (MPP+) with mitochondria. Biochem Biophys Res Commun 159(3):983-90.
Abstract: Inhibition of mitochondrial energy production by MPP+ may be the key step in chemically-induced Parkinson's disease. Tetraphenylboron

(TPB-) markedly enhances the effect of MPP+. Inhibition of respiration and uptake of MPP+ are accelerated, the former by up to two orders of magnitude. TPB increases the final concentration of MPP+ in the matrix by 2-3 fold, insufficient to explain the rapid inhibition of respiration. TPB- lowers the membrane surface potential by only about 20%, but increases the partitioning of MPP+ into organic solvent by one order of magnitude. TPB- also enhances the effect of MPP+ on inverted membranes, reducing the I50 by an order of magnitude. We suggest that TPB- acts by ion pairing with MPP+ to facilitate penetration into mitochondria as well as access to a hydrophobic inhibition site on NADH dehydrogenase.

Rango M, Canesi M, Ghione I, Farabola M, Righini A, Bresolin N, Antonini A, Pezzoli G. 2005 Oct 20. Parkinson' s disease, chronic hydrocarbon exposure and striatal neuronal damage: A 1-H MRS study. Neurotoxicology .

Abstract: Several patients with Parkinson' s disease (PD) reveal an history of chronic exposure to hydrocarbon-solvents. Chronic exposure to hydrocarbon-solvents has been proposed as a risk factor for more severe forms of PD with earlier onset of symptoms and reduced response to dopaminergic therapy. A direct correlation between disease severity and exposure degree has been previously shown. Seven exposed PD patients (two with low degree exposure and five with high degree exposure), 10 unexposed PD patients matched for sex, age and Hoehn and Yahr scale (=3 in the "on" phase), and 10 unexposed PD patients matched for sex, age and l-dopa daily intake instead of disease severity (Hoehn and Yahr scale=3.5 in the "on" phase) were studied. Twenty normal subjects without previous exposure to hydrocarbon-solvents and matched for age and sex with HPD patients were studied for comparison. The purpose of the study was to assess neuronal degeneration in the striatum of exposed vs unexposed PD patients. The authors investigated whether neuronal damage/loss was detectable in the lentiform nucleus measuring N-acetylaspartate (NAA) levels by 1-H MRS. Multiple single voxel MRS water-suppressed spectra were obtained also from the white matter and the occipital lobe. NAA was normal in the lentiform nucleus of patients with low exposure as well as in patients with no exposure whereas it was decreased in PD patients with high degree exposure. White matter and occipital lobe NAA content was normal both in exposed and unexposed PD patients. Clinical expression is more severe in PD patients with previous high degree solvent exposure because of the associated post-synaptic damage of the nigro-striatal pathway.

Reinauer S, Plewig G. 1991 Mar. [Eosinophilia-myalgia syndrome]. Hautarzt 42 (3):137-9.

Abstract: The eosinophilia-myalgia syndrome was first reported from New Mexico, USA, in 1989. Since then, there have been further reports from the USA, Canada and Europe. Patients with the eosinophilia-myalgia syndrome present with myalgias, morbilliform and urticarial rash, oedema, sclerodermiform lesions, fever, pneumonia, fatigue and peripheral eosinophilia (greater than 1,000/mm3). The ultimate cause is postulated to be a contamination produced by Bacterium amyloliquefaciens during the production of L-tryptophan by genetic engineering techniques. HPLC analysis revealed that the causative agent was a condensation product of 1 mole acetaldehyde and 2 moles tryptophan. Clinical and laboratory findings of the eosinophilia-myalgia syndrome, Shulman syndrome and toxic-oil syndrome are discussed.

Reinhardt JW. 1992 Sep. Side-effects: mercury contribution to body burden from dental amalgam. Adv Dent Res 6:110-3.

Abstract: The purpose of this paper is to examine and report on studies that relate mercury levels in human tissues to the presence of dental amalgams, giving special attention to autopsy studies. Until recently, there have been few published studies examining the relationship between dental amalgams and tissue mercury levels. Improved and highly sensitive tissue analysis techniques have made it possible to measure elements in the concentration range of parts per billion. The fact that mercury can be

absorbed and reach toxic levels in human tissues makes any and all exposure to that element of scientific interest. Dental amalgams have long been believed to be of little significance as contributors to the overall body burden of mercury, because the elemental form of mercury is rapidly consumed in the setting reaction of the restoration. Studies showing measurable elemental mercury vapor release from dental amalgams have raised renewed concern about amalgam safety. Mercury vapor absorption occurs through the lungs, with about 80% of the inhaled vapor being absorbed by the lungs and rapidly entering the bloodstream. Following distribution by blood circulation, mercury can enter and remain in certain tissues for longer periods of time, since the half-life of excretion is prolonged. Two of the primary target organs of concern are the central nervous system and kidneys.

Richardson JR, Miller GW. 2004. Acute exposure to Aroclor 1016 or 1260 differentially affects dopamine transporter and vesicular monoamine transporter 2 levels. Toxicol Lett 148(1-2):29-40 .
Abstract: Polychlorinated biphenyls (PCBs) have been shown to specifically target the dopaminergic nervous system, resulting in long-term reduction of striatal dopamine (DA) levels. However, the mechanism(s) by which PCBs exert this effect is not known. Here we report that decreased striatal dopamine levels are observed 1, 7, and 14 days after acute exposure to the common PCB mixtures Aroclor 1016 or 1260. Dopamine transporter (DAT) levels were decreased at all time points in Aroclor 1016 treated animals, and on Days I and 7 in Aroclor 1260 treated animals. Vesicular monoamine transporter 2 (VMAT2) levels were not affected by Aroclor 1016, but were significantly decreased 14 days after exposure to Aroclor 1260. Tyrosine hydroxylase expression, a marker of dopamine neuron integrity, was not significantly affected by PCB exposure at any time. These data suggest that PCB-induced reductions in striatal dopamine may be mediated by alterations in DAT and VMAT2 expression. (C) 2003 Elsevier Ireland Ltd. All rights reserved.

Riederer P, Foley P, Bringmann G, Feineis D, Bruckner R, Gerlach M. 2002. Biochemical and pharmacological characterization of 1-trichloromethyl-1, 2,3,4-tetrahydro-beta-carboline: a biologically relevant neurotoxin? Eur J Pharmacol 442(1-2):1-16.
Abstract: Acute and long-term effects of exposure to reactive compounds as the result of environmental pollution, workplace conditions or dietary intake are suspected to be involved in the etiology of a variety of disorders, including neurodegenerative disorders such as Parkinson's disease. The recognition in 1970s that 1-methyl-4-phenl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxic by-product of illicit meperidine synthesis, elicits parkinsonian symptoms in primates, including man, prompted the search for naturally occurring analogs which might be involved in human disease. It has been suggested that one candidate, 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo), a potent dopaminergic neurotoxin, might be formed endogenously in humans following the administration of the hypnotic chloral hydrate or after the exposure to the industrial solvent trichloroethylene, Such spontaneous formation has, indeed, been recently reported. The biochemical and pharmacological characteristics of TaClo and related compounds are thus reviewed here, and their potential significance for human neurodegenerative disease discussed. (C) 2002 Elsevier Science B.V. All rights reserved.

Sagvolden T, Johansen EB, Aase H, Russell VA . 2005. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav Brain Sci 28(3):397-+.
Abstract: Attention-deficit/hyperactivity disorder (ADHD) is currently defined as a cognitive/behavioral developmental disorder where all clinical criteria are behavioral. Inattentiveness, overactivity, and impulsiveness are presently regarded as the main clinical symptoms. The dynamic developmental behavioral theory is based on the hypothesis that altered

dopaminergic function plays a pivotal role by failing to modulate nondopaminergic (primarily glutamate and GABA) signal transmission appropriately. A hypofunctioning mesolimbic dopamine branch produces altered reinforcement of behavior and deficient extinction of previously reinforced behavior. This gives rise to delay aversion, development of hyperactivity in novel situations, impulsiveness, deficient sustained attention, increased behavioral variability, and failure to "inhibit" responses ("disinhibition"). A hypofunctioning mesocortical dopamine branch will cause attention response deficiencies (deficient orienting responses, impaired saccadic eye movements, and poorer attention responses toward a target) and poor behavioral planning (poor executive functions). A hypofunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions and deficient nondeclarative habit learning and memory. These impairments will give rise to apparent developmental delay, clumsiness, neurological "soft signs," and a "failure to inhibit" responses when quick reactions are required. Hypofunctioning dopamine branches represent the main individual predispositions in the present theory. The theory predicts that behavior and symptoms in ADHD result from the interplay between individual predispositions and the surroundings. The exact ADHD symptoms at a particular time in fife will vary and be influenced by factors having positive or negative effects on symptom development. Altered or deficient learning and motor functions will produce special needs for optimal parenting and societal styles. Medication will to some degree normalize the underlying dopamine dysfunction and reduce the special needs of these children. The theory describes how individual predispositions interact with these conditions to produce behavioral, emotional, and cognitive effects that can turn into relatively stable behavioral patterns.

Samir AM. 2000. The response of benthic foraminifera and ostracods to various pollution sources: A study from two lagoons in Egypt. Journal of Foraminiferal Research 30(2):83-98.
Abstract: A study of foraminiferal assemblages was carried out at two Egyptian Nile Delta lagoons. Analysis of surficial sediment samples from Manzalah Lagoon shows enrichment in heavy metals (Pb, Zn, Cu, Cr and Cd). The environment has become so lethal to foraminifera that no species can currently survive. Among ostracods, only one species (Cyprideis torosa) was found living and able to invade the polluted lagoon region. Samples from Edku Lagoon, which receives only agricultural drainage water, show heavy metal concentrations close to natural baseline levels, and yield living foraminifera, The frequent occurrence of deformed specimens in Manzalah Lagoon, comparable to Edku Lagoon, reveals that: (1) benthic foraminifera are more sensitive to industrial wastes containing heavy metals; (2) agricultural wastes do not significantly harm benthic foraminifera; (3) Ammonia beccarii forma parkinsoniana is less resistant to pollution than forma tepida; (4) morphological abnormalities of the foraminiferal tests depend upon the nature of the pollutant; and (5) benthic foraminifera are less tolerant to pollution than ostracods and molluscs.

Sandyk R, Gillman MA. 1984. Motor dysfunction following chronic exposure to a fluoroalkane solvent mixture containing nitromethane. Eur Neurol 23(6): 479-81.
Abstract: We report the occurrence of a partially reversible Parkinson-like extrapyramidal syndrome in a woman chronically exposed to vapours from an industrial solvent mixture based on trichlorotrifluoroethane and nitromethane. The fluoroalkane group of compounds has not been previously reported to produce such effects in man, but mixtures containing nitromethane may not be innocent. Under certain industrial conditions the conversion of nitromethane to methylisocyanide may result in toxicity particularly in the basal ganglia and cerebellum following chronic low level exposure.

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?

Schinelli S, Zuddas A, Kopin IJ, Barker JL, di Porzio U. 1988 Jun. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine metabolism and 1-methyl-4-phenylpyridinium uptake in dissociated cell cultures from the embryonic mesencephalon. J Neurochem 50(6):1900-7.
Abstract: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant found in a synthetic illicit drug, can elicit in humans and monkeys a severe extrapyramidal syndrome similar to Parkinson's disease. It also induces alterations of the dopamine (DA) pathways in rodents. MPTP neurotoxicity requires its enzymatic transformation into 1-methyl-4-phenylpyridinium (MPP+) by monoamine oxidase followed by its concentration into target cells, the DA neurons. Here, we show that mesencephalic glial cells from the mouse embryo can take up MPTP in vitro, transform it into MPP+, and release it into the culture medium. MPTP is not taken up by neurons from either the mesencephalon or the striatum in vitro (8 days in serum-free conditions). However, mesencephalic neurons in culture revealed a high-affinity uptake mechanism for the metabolite MPP+, similar to that for DA. The affinity (Km) for DA uptake is fivefold higher than that for MPP+ (0.2 and 1.1 microM, respectively), whereas the number of uptake sites for MPP+ is double (Vmax = 25 and

55 pmol/mg of protein/min for DA and MPP+, respectively). Mazindol, a DA uptake inhibitor, blocks the uptake of DA and MPP+ equally well under these conditions. Moreover, by competition experiments, the two molecules appear to use the same carrier(s) to enter DA neurons. Small concentrations of MPP+ are also taken up by striatal neurons in vitro. The amount taken up represented less than 10% of the MPP+ uptake in mesencephalic neurons. Depolarization induced by veratridine released comparable proportions of labeled DA and MPP+ from mesencephalic cultures.(ABSTRACT TRUNCATED AT 250 WORDS)

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.

Scriabine A, Pan M. 1988. Ca2+ antagonists and inhibitory effects of dopamine on isolated rabbit ear artery. J Cardiovasc Pharmacol 12 Suppl 4:S107-12.
Abstract: Rabbit ear arteries were isolated and perfused with Krebs-bicarbonate buffer. Brief periods of supramaximal nerve stimulation caused reproducible constriction of the arteries, which was inhibited by dopamine (EC50 approximately equal to 0.1 microM). Verapamil or flunarizine (at 1 or 5 microM) antagonized this inhibitory effect of dopamine. The maximal effect of verapamil, 5 microM was reached after 8 min and that of flunarizine, 5 microM after 40 min of perfusion with the drug. The antagonism of dopamine by verapamil, even at 5 microM, was incomplete (approximately equal to 80%), whereas flunarizine, 5 microM completely antagonized the effect of dopamine. Nitrendipine, nimodipine, or nisoldipine, at either 1 or 5 microM, or solvent (ethanol, 0.03%) had no significant effect on dopamine-induced inhibition of vasoconstriction even after perfusion for 40 min. Antagonism of dopamine at central synapses may conceivably explain reported Parkinsonian side effects of flunarizine. Our results suggest a mechanism for the tendency of flunarizine to cause Parkinsonism and an explanation why 1,4-dihydropyridines are not likely to have this side effect.

Seegal RF. 1996. Epidemiological and laboratory evidence of PCB-induced neurotoxicity. Crit Rev Toxicol 26(6):709-737.
Abstract: The purpose of this review is to provide a selective, but critical, assessment of important findings derived from both epidemiological and laboratory studies suggesting that: (1) exposure to polychlorinated biphenyls (PCBs) and related halogenated aromatic hydrocarbons induces significant neurological and behavioral dysfunctions in humans and laboratory animals, particularly following exposure during gestation and lactation; (2) the neurochemical actions of PCBs depend on their structure and the developmental status of the animal at the time of exposure; and (3) the mechanisms responsible for these changes may involve alterations in basic cellular signaling processes and endocrine function that influence the synthesis and activity of important central nervous system

neurotransmitters, the organization of the developing brain, and the behavioral responses to these environmental contaminants.

Seegal RF, Bush B, Brosch KO. 1991. Comparison of effects of Aroclor-1016 and Aroclor-1260 on nonhuman primate catecholamine function. Toxicology 66 (2):145-163.
Abstract: Adult male non-human primates, Macaca nemestrina, were orally-exposed to corn oil or corn oil containing either Aroclor 1016 or 1260 at doses of 0.8, 1.6 or 3.2 mg/(kg.day) for 20 weeks. Brain concentrations of biogenic amines and individual PCB congeners were determined following exposure. Aroclor 1016 significantly decreased concentrations of dopamine and its metabolites in the caudate, putamen, substantia nigra and hypothalamus but did not alter neurotransmitter or metabolite concentrations in the globus pallidus and hippocampus. Total PCB concentrations ranged from 1 to 5 ppm with only three congeners detected (2,4,4'; 2,4,2',4' and 2,5,2',5') making up, on average, 72%, 18% and 7% respectively of the total residue in brain. There were no discernible differences in the congener make-up between brain regions. Aroclor 1260 reduced dopamine concentrations in the caudate, putamen and hypothalamus but produced no effects in the substantia nigra, globus pallidus or hippocampus. Aroclor 1260 concentrations ranged from 18 to 28 ppm with the highest levels found in the hippocampus. Of the congeners that made up more than 5% of the total residue in brain, all were hexa- and heptachlorinated di-ortho-substituted congeners. There were no discernible differences in congener make-up between brain regions. We conclude that: (1) ortho-substituted non-planar congeners are responsible for the observed changes in neurochemical function; (2) both Aroclor 1016 and Aroclor 1260 decrease dopamine concentrations by similar mechanisms; and (3) based on differences in brain concentrations of Aroclor 1260 congeners compared to Aroclor 1016 congeners, lightly-chlorinated congeners are more effective in reducing central dopamine concentrations than are the more highly chlorinated congeners.

Seegal RF, Bush B, Brosch KO. 1991. Subchronic exposure of the adult-rat to Aroclor 1254 yields regionally-specific changes in central dopaminergic function. Neurotoxicology 12(1):55-66.
Abstract: Laboratory rats were exposed to chow adulterated with either 500 or 1000 ppm Aroclor 1254 for 30 days. Analysis of biogenic amines and their metabolites in the dorsal frontal cortex, lateral olfactory tract, striatum, basal hypothalamus, hippocampus and brainstem revealed significant decreases in dopamine concentrations and metabolism in only the striatum and lateral olfactory tract. Concentrations of individual PCB congeners in the striatum, lateral olfactory tract and hippocampus were measured by gas chromatography with electron capture detection. Neither total concentration nor variations in concentrations of individual congeners between regions could explain this regional specificity. The susceptibility of the striatum and lateral olfactory tract to insult by PCBs may be due to their innervation by midbrain dopaminergic neurons which have been shown to be particularly sensitive to insult from environmental, infectious and pharmacologic agents.

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.

Shamovsky IL, Riopelle RJ, Ross GM. 2001. Ab initio studies on the mechanism of tyrosine coupling. Journal of Physical Chemistry a 105(6):1061-1070.
Abstract: Oxidative stress is considered to be a major contributor to dysfunction in a host of disease states. Reactive oxygen species (ROS) mediate distinct oxidative alterations in biopolymers, including DNA, proteins, lipids, and lipoproteins. Currently, the mechanisms of biochemical reactions underlying oxidative stress are poorly understood because of the instability of ROS. One of the consequences of oxidative stress is one-electron oxidation of tyrosine (Tyr) residues in proteins, which represents a hallmark of this insult and is implicated in the pathogenesis of a number of pathological processes leading to atherosclerosis, inflammatory conditions, multiple system atrophy and several neurodegenerative diseases. Major products of oxidation of Tyr include protein-bound dityrosine and isodityrosine. In this report, the mechanism of tyrosine coupling (including structure and stability of a number of proposed reaction intermediates) is studied by high-level density functional and conventional ab initio methods including B3LYP, MP2, CASSCF, and CASPT2. It is demonstrated that dityrosine and isodityrosine are the most stable structures at all theoretical levels applied. In addition to classical structures of the reaction intermediates, evidence is found for a novel transient structure of Tyr dimer, stacked dityrosyl. This dimer is predicted to exist because of strong electron correlation between two tyrosyl moieties. The counterpoise corrected energy of stacked dityrosyl is below the energy of two tyrosyl radicals by about 95 kJ/mol at the PUMP2/6-31** level. High proton affinity of tyrosyl radical (about 9.4 eV) suggests that positively charged amino acids in the vicinity of a solvent-exposed Tyr residue may increase the probability of tyrosine coupling.

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.

Spooren Wpjm, Vassout A, Waldmeier P, Gentsch C. 1998. Differences in pre- and post-synaptic sensitivity to apomorphine between saline and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated C57BL/6 mice as reflected in climbing activity. Eur J Pharmacol 353(1):1-4.
Abstract: The climbing behaviour after low doses (0.05, 0.1 and 0.2 mg/kg) or a high dose (1.5 mg/kg) of apomorphine was studied in saline or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated C57BL/6 mice. Following a 3-week recovery from two injections of saline or MPTP (50 mg/kg inter-injection period: 72 h), mice were randomly selected for determinations of contents of neurotransmitters and metabolites (dopamine, homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), serotonin (5-hydroxytryptamine, 5-HT) and 5-hydroxyindole-3-acetic acid (5-HIAA)) or the apomorphine-induced climbing paradigm. For the climbing experiment, the animals were habituated for 60 min to metal climbing cylinders after which they received a subcutaneous injection of apomorphine or its solvent. Subsequently, the animals were placed back in the cylinders and their climbing scores were recorded every 5 min for 60 min. The biochemical data indicated that striatal levels of dopamine, DOPAC and HVA were significantly reduced following MPTP-treatment whereas striatal 5-HT and 5-HIAA levels were unaffected. In the climbing paradigm saline and MPTP-treated C57BL/6 mice responded diametrically opposite to low doses of apomorphine: 0.1 and 0.2 mg/kg apomorphine reduced the climbing score in saline-treated mice as compared to saline injections whereas 0.2 mg/kg apomorphine increased the climbing score in MPTP-treated mice. A relatively high dose of apomorphine (1.5 mg/kg) increased the climbing score in both saline- and MPTP-treated mice. However, the climbing score was significantly higher in MPTP-treated mice than in saline-treated mice. These data suggest that MPTP-treated mice lack pre-synaptic dopamine receptors and have an increased post-synaptic sensitivity for apomorphine which is in agreement with the fact that MPTP selectively affects the dopaminergic nigro-striatal pathway which then results in an up-regulation of post-synaptic receptors. (C) 1998 Elsevier Science B.V. All rights reserved.

Srisailam S, Krishnaswamy T, Kumar TKS, Rajalingam D, Kathir KM, Sheu HS, Jan FJ, Chao PC, Yu C. 2003. Amyloid-like fibril formation in an all beta-barrel protein - Partially structured intermediate state(s) is a precursor for fibril formation. J Biol Chem 278(20):17701-17709.
Abstract: Acidic fibroblast growth factor from newt (Notopthalmus viridescens) is a similar to15-kDa, all beta-sheet protein devoid of disulfide bonds. In the present study, we investigate the effects of 2,2,2-trifluoroethanol (TFE) on the structure of newt acidic fibroblast growth factor (nFGF-1). The protein aggregates maximally in 10% (v/v) TFE. Congo red and thioflavin T binding experiments suggest that the aggregates induced by TFE have properties resembling the amyloid fibrils. Transmission electron microscopy and x-ray fiber diffraction data show that the fibrils (induced by TFE) are straight, unbranched, and have a cross-beta structure with an average diameter of 10-15 Angstrom. Preformed fibrils (induced by TFE) of nFGF-1 are observed to seed amyloid-like fibril formation in solutions containing the protein (nFGF-1) in the native beta-barrel conformation. Fluorescence, far-UV CD, anilino-8-napthalene sulfonate binding, multidimensional NMR, and Fourier transformed infrared spectroscopy data reveal that formation of a partially structured intermediate state(s) precedes the onset of the fibrillation process. The native beta-barrel structure of nFGF-1 appears to be disrupted in the partially structured intermediate state(s). The protein in the partially structured intermediate state(s) is found to be "sticky" with a solvent-exposed non-polar surface(s). Amyloid fibril formation appears to occur due to coalescence of the protein in the partially structured

intermediate state(s) through solvent-exposed non-polar surfaces and intermolecular beta-sheet formation among the extended, linear beta-strands in the protein.

Steenland K, Hein MJ, Cassinelli RT, Prince MM, Nilsen NB, Whelan EA, Waters MA, Ruder AM, Schnorr TM. 2006. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. Epidemiology 17(1):8-13.
Abstract: Background: Production of polychlorinated biphenyls (PCBs) ended in the United States in the 1970s, but PCBs persist in the environment and are detectable in the blood of approximately 80% of Americans over age 50. PCBs decrease dopamine levels in rats and monkeys. Loss of dopamine is the hallmark of Parkinson disease, a neurodegenerative disease. There are no epidemiologic studies of PCBs and neurodegenerative disease. Methods: We conducted a retrospective mortality study of 17,321 PCB-exposed workers to determine whether mortality from Parkinson disease, dementia, and amyotrophic lateral sclerosis was elevated compared with the U.S. population. All workers had a least 90 days employment in 1 of 3 electrical capacitor plants using PCBs from the 1940s to the 1970s. PCB serum levels from a sample of these workers in the 1970s were approximately 10 times the level of community controls. Results: We found no overall excess of Parkinson disease, amyotrophic lateral sclerosis, or dementia in the PCB-exposed cohort (standardized mortality ratios [SMRs]-1.40, 1.11, and 1.26, respectively, and number of deaths-14, 10, and 28 respectively). However, sex-specific analyses revealed that women had an excess of amyotrophic lateral sclerosis (SMR-2.26; 95% confidence interval [CI] = 1.08-4.15; 10 deaths). Furthermore, among highly exposed women (defined by a job-exposure matrix), we found an excess of Parkinson disease (SMR-2.95; 95% CI = 1.08-6.42; 6 deaths) and dementia (SMR-2.04; 95% CI = 1.12-3.43; 14 deaths). Conclusions: Our data are limited due to small numbers and reliance on mortality rather than incidence data, but are suggestive of an effect of PCBs on neurodegenerative disease for women. The literature does not offer an explanation for why women would be more affected than men by PCB exposure for these outcomes.

Stoppini M, Andreola A, Foresti G, Bellotti V. 2004. Neurodegenerative diseases caused by protein aggregation: a phenomenon at the borderline between molecular evolution and ageing. Pharmacol Res 50(4):419-431.
Abstract: A process of protein aggregation that causes intracellular or extracellular accumulation of insoluble protein deposits causes many important neurodegenerative diseases associated with the ageing. The recognition that protein aggregation plays a prominent role in pathogenesis of important pathologies such as Alzheimer's and Parkinson's diseases prompted the scientific community to focus on the molecular mechanism of protein aggregation. Many proteins with sophisticated functions can self-aggregate because their folding is complicate and abnormal intermolecular contacts can predominate over the normal intramolecular interactions. The review of biochemical functional and pathogenic implications attributed to alpha synuclein, Abeta peptide, presenilin and apoE highlights for these proteins a common conformational plasticity and the capacity to adapt their secondary structure to surrounding solvent as well as to the contacted ligands. Their functions are not fully elucidated but there is an elevated number of metabolic pathways in which apparently they are involved as well as they generate functional contact with a remarkable number of other proteins. The mechanism by which alpha synuclein and Abeta protein make fibrils is an example of conformational plasticity because both these polypeptides can visit a coil or helical structure, but otherwise they convert into a pathogenic beta sheet structure highly suitable for polymerisation and fibril formation. The emerging question in the puzzling pathogenic basis of these diseases is if protein aggregation associated with ageing has a role in molecular evolution of the species or if it just represents a calculated drawback. (C) 2004 Elsevier Ltd. All rights reserved.

Suleiman MK, Bhat NR. 2003. Performance of ornamental plants in bioremediated

soil. Arid Land Research and Management 17(2):169-176.
Abstract: At the conclusion of the Gulf War in 1991, more than 700 gushing wells discharged over 60 million barrels of crude oil, forming nearly 300 oil lakes that covered more than 49 km(2) of land surface. This contaminated approximately 40 million tons of soil. An additional 700 km(2) of terrestrial land was contaminated by oily mist fallout. Kuwait Institute for Scientific Research successfully tested and standardized bioremediation technology to significantly reduce petroleum oil contaminants in the soil. Preliminary results suggested that the bioremediated soil was capable of supporting plant growth without adverse effects. In the present study, growth of a number of ornamental plants in bioremediated soil was compared with that in normal agricultural soil to assess the suitability of bioremediated soil for use in landscape/greenery projects in Kuwait. Results indicated that the bioremediated soil did not affect the establishment of test plants, but influenced their growth to varying extents. Height increments in the bioremediated soil during the first 12 months in Dalbergia sissoo, Prosopis chiliensis, Olea europaea, Parkinsonia aculeata, and Conocarpus lancifolius was 6.2 to 72.9% higher than those in agricultural soil. In contrast, it adversely affected the height growth in Callistemin viminalis and Acacia acuminata and had no influence on plant height in Pithecellobium dulce. The average height increment in three shrubs (Clerodendron inerme, Bougainvillea glabra, and Vitex negundo) out of the six shrubs tested in the study, was two to three times higher in bioremediated soil than in agricultural soil. Growths were adversely affected in the three others (Bougainvillea sp., Simmondsia chinensis and Thevitia nerifolia). Based on the growth data, ornamental plants tested in the study were grouped into three categories: the first group consisted of plants whose growth was promoted in bioremediated soil; the second group included plants whose growth was not affected; and the third group comprised species that were sensitive to petroleum oil pollutants.

Sun DS, Chang HH. 2003. Differential regulation of JNK in caspase-3-mediated apoptosis of MPP+-treated primary cortical neurons . Cell Biol Int 27(9): 769-777.
Abstract: MPTP (1-methyl-1,2,3,6-tetrahydropyridine), a chemical contaminant of synthetic heroin, induces neuropathological changes with clinical features similar to idiopathic Parkinson's disease. The mechanism by which MPTP and its metabolite MPP+ (1-methyl-4-phenylpyridinium) induces neuronal cell death remains unclear. We employed primary cortical/telencephalon neuronal cultures to investigate the potential role of caspase and stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK) pathways in MPP+-induced neuronal death. DNA fragmentation and caspase-3 activity analysis showed that cortical neuronal cells underwent apoptosis after MPP+ treatment. However, a basal level of apoptotic cells was also observed in untreated cultures. Interestingly, JNK activity increased in untreated cultures over time, whereas it was down-regulated after MPP+ treatment. This indicates that the JNK pathways could be differentially regulated in different apoptotic processes. (C) 2003 Published by Elsevier Ltd.

Takakubo F, Yamamoto M, Ogawa N, Yamashita Y, Mizuno Y, Kondo I. 1996. Genetic association between cytochrome P450IA1 gene and susceptibility to Parkinson's disease. J Neural Transm 103(7):843-849.
Abstract: Idiopathic Parkinson's disease (PD) is a multifactorial neurodegenerative disorder resulting from environmental factors acting on genetically susceptible individuals with normal aging. Cytochrome P450IA1 is a dioxin-inducible enzyme which is responsible for the activation of procarcinogens and environmental pollutants, such as benzo[a]pyrene and other aromatic hydrocarbons. The frequencies of polymorphic alleles of cytochrome P450IA1 gene (CYPIA1) were studied in 126 unrelated patients with PD in comparison with 176 healthy Japanese. The frequency of the Msp I polymorphic allele, a variant of CYPIA1 (m2), was significantly higher in patients with PD (0.444) than in controls (0.349). The risk of PD in homozygotes for m2 was 2.34-fold greater than homozygotes for the wild-type, m1. The relative risk for PD in homozygotes for CYPIA1Val was 6.54-

fold higher than in homozygotes for the wild type (CYPIA1Ile)($p < 0.001$). These results strongly suggest that the CYPIA1 might be one of the susceptibility genes for PD.

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.

Toronyi E, Hamar J, Magyar K, Szende B. 2002 Feb. Antiapoptotic effect of (-)-deprenyl in rat kidney after ischemia-reperfusion . Med Sci Monit 8 (2):BR65-8.
Abstract: BACKGROUND: Since apoptosis of renal tubular cells is the basis of the damage caused by ischaemia-reperfusion, the antiapoptotic effect on kidney tubular epithelial cells of the monoamino oxidase-B (MAO-B) inhibitor (-) deprenyl (selegiline), known neuroprotective agent, with antiapoptotic properties, was studied in a rat model. MATERIAL/METHODS: Warm renal ischaemia was caused by clamping the left renal artery of rats for 30 minutes. With the start of reperfusion 0.015 mg/kg, 0.15 mg/kg and 1.5 mg/kg of (-)-deprenyl was injected simultaneously into the carotid artery of the animals, respectively. Five rats served as control, in which renal artery clamping was performed, but the rats were only treated with the solvent (physiological saline). After 6 hours of reperfusion the rats were exsanguinated and the kidneys were histologically examined. RESULTS: Severe tubular damage characterised by apoptosis was found in the kidneys of the untreated rats. Apoptosis was verified on the basis of morphological features, methylgreen-pyronin staining and TUNEL reaction. (-)-Deprenyl diminished dose-dependently the apoptotic damage, 0.15 mg/kg being the most effective dose. The same dose of (-)-Deprenyl is used in the therapy of human Parkinson's disease. CONCLUSIONS: Our findings suggest, that (-)-deprenyl might have an impact on decreasing renal injury also in case of human cadaveric renal transplantation.

Tosk JM, Farag M, Ho JY, Lee CC, Maximos BB, Yung HH. 1996. The effects of nerve growth factor and ganglioside GM(1) on the anti-proliferative activity of cocaine in PC12 cells. Life Sci 59(20):1731-1737.
Abstract: The anti-proliferative activity of cocaine was determined in PC12 pheochromocytoma cells. The effects of nerve growth factor (NGF) and ganglioside GM(1) (GM(1)) on the toxicity of this stimulant of abuse was examined over a period of 72 h. Cocaine (40 mu M-320 mu M) exhibited a dose-dependent inhibition of cellular proliferation as determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) reduction. While NGF (100 ng/ml) and GM(1) (100 mu M) alone partially reversed the cocaine-induced inhibition of proliferation, the combination of NGF and GM(1) afforded additional protection that was greater than that of either agent individually.

Uitti RJ, Snow BJ, Shinotoh H, Vingerhoets FJG, Hayward M, Hashimoto S, Richmond J, Markey SP, Markey CJ, Calne DB. 1994. Parkinsonism induced by solvent abuse. Ann Neurol 35(5):616-619.
Abstract: We report the first description of a patient with parkinsonism induced by solvent abuse. Our patient developed parkinsonism acutely, following heavy abuse of lacquer thinner. Her clinical deficits were indistinguishable from idiopathic parkinsonism (Parkinson's disease) and she responded to levodopa. Parkinsonism has persisted for more than 3 months. Brain computed tomography was normal. Positron emission

tomographic studies showed normal fluorodopa uptake and reduced raclopride binding, indicating an unusual disturbance of striatal dopaminergic function. This patient suggests that organic solvents may cause parkinsonism in susceptible individuals.

Vaglini F, Fascetti F, Tedeschi D, Cavalletti M, Fornai F, Corsini GU. 1996. Striatal MPP+ levels do not necessarily correlate with striatal dopamine levels after MPTP treatment in mice. Neurodegeneration 5(2):129-136.
Abstract: The present study offers confirmation of the fact that an MAO-B inhibitor, (-) deprenyl and a DA uptake blocker, GBR-129D9, prevent MPTP-induced striatal DA decrease. This protective effect is accompanied by an almost complete prevention of MPP(+) production induced by (-) deprenyl and an accelerated MPP(+) clearance induced by GBR-12909 within the striatum. Similarly, the MPTP toxicity enhancers, DDC and acetaldehyde, both increase striatal MPP(+) levels, as previously reported. On the contrary, the treatment with MK 801, although uneffective in preventing the long-term MPTP-induced striatal DA decrease, causes an increase in the striatal amount of MPP(+). In a similar way, the administration of nicotine in combination with MPTP produces a significant increase in the levels of striatal MPP(+), which does not elicit any effect on striatal DA. The effect of clonidine is consistent with these results and in sharp contrast with the current belief that a direct relationship exists between striatal MPP(+) concentrations and the degree of MPTP-induced depletion of striatal DA. In this study, using different treatments, we failed to confirm the correlation between MPP(+) striatal levels and dopaminergic lesions after MPTP administration in mice. We suggest that this correlation is not a rule and exceptions may depend on a different compartimentalization of the toxic metabolite. (C) 1996 Academic Press Limited.

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, Gasparini M, Brusa L, Meco G. 2000. A possible association between exposure to n-hexane and parkinsonism. Neurological Sciences 21(1): 49-52.
Abstract: Recently, some case-control studies and case reports have shown an association between solvent exposure and parkinsonisms. We present a 55-year-old male parkinsonian patient with chronic exposure to n-hexane for 17 years. The results of neurophysiological (electromyography, evoked potentials), neuroradiological (MRI) and neuropsychological tests performed on the patient suggest a role of this solvent at the level of the central nervous system. Biological susceptibility to neurotoxic compounds is discussed briefly.

Vernay D, Eschalier A, Durif F, Aumaitre O, Rigal B, Ben Sadoun A, Fialip J, Marty H, Philip E, Bougerolle AM, et al. 1989 Nov-Dec. [Salsolinol, an endogenous molecule. Possible implications in alcoholism, Parkinson's disease and

pain]. Encephale 15(6):511-6.
Abstract: Salsolinol can be formed either by condensation of dopamine with acetaldehyde, or by condensation of dopamine with pyruvic acid followed by decarboxylation. Salsolinol has a complex pharmacologic profile. Its opium-like activity may be related to alcohol dependency and to the effectiveness of naloxone during acute alcohol intoxication. Because they had noticed that alcoholism and Parkinson's disease rarely coexist, the authors undertook a study to confirm this fact and attempt to explain it by implicating salsolinol. Urinary excretion of salsolinol was found to increase following ingestion of alcohol, as well as in Parkinson patients under L-dopa treatment. The authors also found that urinary salsolinol was very low in untreated patients with Parkinson's disease. Salsolinol was detected in a number of foods and beverages. Separate assays of enantiomeres showed that the S enantiomere predominates in some foods whereas the R enantiomere is more abundant in humans. Lastly, the antinociceptive effects of salsolinol and its enantiomeres were studied in mice and antidepressant effects were evidenced using predictive tests.

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.

Weiss B, Landrigan PJ. 2000 Jun. The developing brain and the environment: an introduction. Environ Health Perspect 108 Suppl 3:373-4.
Abstract: mental retardation: timing and thresholds; (italic)b(/italic)) endocrine dysfunction and developmental disabilities: dose and target implications; (italic)c(/italic)) attention-deficit disorder-ADHD and learning disabilities; and (italic)d(/italic)) new horizons: extending the boundaries. Support for the Rochester conference came from both public and private sources. The National Institute of Environmental Health Sciences (NIEHS), the National Institute of Child Health and Human Development, and the EPA represented the federal government. The conference also received grants from several foundations: the Jennifer Altman Foundation, the Heinz Family Foundation, the National Alliance for Autism Research, the Violence Research Foundation, the Wacker Foundation, and the Winslow Foundation. The second of these conferences helped launch a new Center for Children's Health and the Environment at the Mount Sinai School of Medicine. It was held in New York City on 24-25 May 1999, and was convened specifically to consider the intersection between neurodevelopmental impairment, environmental chemicals, and prevention. Over 300 health scientists, pediatricians, and public health professionals examined the growing body of evidence linking environmental toxins to neurobehavioral disorders. The conference title was Environmental Influences on Children: Brain, Development, and Behavior. The conference began by reviewing well-known examples of deleterious effects of environmental chemicals, including lead and PCBs, on children's brains. The conferees then considered the potential impact of environmental chemicals on neurological disorders with particular focus on ADHD, autism, and Parkinson's disease. The inclusion of Parkinson's disease was intended to signal the notion that exposures in early life may have an influence on the evolution of

neurological disease in later life. Support for the Mount Sinai conference came from the Superfund Basic Research Program (NIEHS); The Pew Charitable Trusts; the Institute for Health and the Environment at the University of Albany School of Public Health; the Agency for Toxic Substances and Disease Research (ATSDR); the Ambulatory Pediatric Association; Myron A. Mehlman, PhD; the National Center for Environmental Assessment (EPA); the National Center for Environmental Health (CDC); the National Institute of Child Health and Human Development; the Office of Children's Health Protection (EPA); Physicians for Social Responsibility; The New York Academy of Medicine; The New York Community Trust; and the Wallace Genetic Foundation. The impact of environmental toxins on children's health has become a topic of major concern in the federal government. Eight new research centers in children's environmental health have been established in the past 2 years with joint funding from EPA and NIEHS. Clinical units that specialize in the treatment of children with environmentally induced illness have been developed across the nation with grant support from ATSDR. The American Academy of Pediatrics has just published its (italic)Handbook of Pediatric Environmental Health (/italic)((italic)17(/italic)), the "Green Book," which is available to pediatricians throughout the Americas. Children's environmental health has climbed to a critical position as we launch the new millennium. This monograph marks a significant milestone in the evolution of this emerging discipline.

Wetmur JG, Casals J, Elizan TS. 1984 Nov-Dec. DNA binding protein profiles in Alzheimer's disease. J Neurol Sci 66(2-3):201-8.
Abstract: Eleven frozen autopsy specimens from cerebral cortex were tested for DNA-binding protein profiles. Six were Alzheimer's disease (AD) brains, 1 was Parkinson's/senile dementia of the Alzheimer's type and 4 were age-matched control brains. Proteins were extracted in a guanidine thiocyanate-containing solvent and freed of all nucleic acids by density gradient sedimentation. The proteins were separated by sodium dodecyl sulfate gel electrophoresis and transferred to nitrocellulose by electroblotting under conditions which favor renaturation of proteins containing only one type of polypeptide. The nitrocellulose was treated with partially denatured radiolabeled DNA, washed and subjected to autoradiography. An Mr = 43 000 (43 K) DNA-binding protein was detected in 5 of the 6 AD brains and was found to be absent or at least greatly reduced in any of the other 6 brains. No other DNA-binding proteins were found which could be associated with AD brains. The nature of the 43 K protein has yet to be determined.

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.

Zeaponce Y, Baldwin RM, Laruelle M, Wang SY, Neumeyer JL, Innis RB. 1995. Simplified multidose preparation of iodine-123-beta-cit - a marker for dopamine transporters. J Nucl Med 36(3):525-529.
Abstract: Iodine-123-beta-CIT is a SPECT radioligand for dopamine and 5-HT transporters with potential use in Parkinson's disease, schizophrenia and cocaine addiction studies. At present, preparation of no-carrier-added (NCA) [I-123]beta-CIT is achieved by iododestannylation of a trialkylstannyl precursor with sodium [I-123]iodide in the presence of oxidizing agent, followed by preparative HPLC. The purpose of this study was to develop a faster and simpler method for the routine preparation of this radiopharmaceutical. Methods: Purification of the labeled compound was accomplished by solid phase extraction (SPE) with a C-18 Sep-Pak Light cartridge, which removed unreacted iodide, reaction reagents, polar side products and tributylstannyl precursor. The tributylstannyl precursor was preferred as starting material over the trimethylstannyl precursor due to its higher lipophilicity, allowing better separation of the labeled product and precursor. A TLC method was developed to assess the radiochemical purity of the final product. Results: The method produced [I-123]beta-CIT in high radiochemical yields (75% +/- 4%), with high radiochemical purity (greater than or equal to 98%) and specific activity (>67000 Ci/mmole), in 1.5 hr. The final formulation was sterile and pyrogen free. Conclusion: The results obtained by solid phase extraction are consistent with those obtained by the HPLC method; with the advantage that the SPE method does not require solvent extraction, evaporation under reduced pressure or HPLC purification.

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.