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# **Aspects of Parkinson's disease. Epidemiology, risk factors and ECT in advanced disease**

Per-Arne Fall



**FACULTY OF HEALTH SCIENCES**  
**LINKÖPINGS UNIVERSITET**

Division of Geriatrics, Department of Neuroscience and Locomotion,  
Faculty of Health Sciences, S-581 85 Linköping, Sweden  
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Picture on cover:  
Signature of a now deceased patient before, during, and after an ECT series.  
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*The advanced Parkinson patient and perhaps  
the author move forward with small strenuous steps*

*To my beloved Birgitta*

## ABSTRACT

The purpose was to investigate some aspects of epidemiology, risk factors and treatment with ECT in advanced Parkinson's disease (PD).

In study I, we performed a descriptive epidemiologic population-based survey in the Central Health Care District in Östergötland in south-east Sweden, with a population of almost 150,000 inhabitants 1989. The case finding was accomplished in three ways: 1. Collection of all prescriptions for Parkinson's disease. 2. Search in medical files. 3. Checking with all nursing homes in the area. The crude prevalence was found to be 115 per 100,000 inhabitants. When we used the European Standard Population as a tool for easy comparisons of PD prevalence between different areas and time periods 76 PD-cases per 100,000 inhabitants were found. The corresponding incidences were 11.0 (crude) and 7.9 (age standardised) per 100,000 person-years. Mean age at onset was 65.6. A low prevalence and a high age at onset suggested that e.g. environmental factors could influence the occurrence of PD, and the results implies that only few such factors were present in the investigated area.

The findings led to study II, a case-control study which investigated the possible impact of nutritional and environmental risk factors for idiopathic Parkinson's disease (IP), including 113 cases and 263 control subjects. Dietary, drinking, and smoking habits, as well as previous occupation, were requested in a structured questionnaire. No increased risk was found for any of the nutrients. A reduced risk was found for coffee, wine, and spirits but also for broiled meat, smoked ham or meat, eggs, French loaf or white bread, and tomatoes. These findings could indicate an antioxidant effect. Frequency of preceding and present smoking was reduced in IP patients. Possible mechanisms are discussed. Various occupational groups and exposures were analysed and increased risks of IP in men were found for agricultural work, pesticide exposure, male carpenters, and in female cleaners.

In advanced PD there is a need for further therapeutic improvements, and electroconvulsive therapy (ECT) is one insufficiently explored and evaluated method. In study III ECT 16 non-depressed, non-demented PD patients with advanced disease were treated with ECT. In all patients an antiparkinsonian effect of ECT was seen, lasting between a few days and 18 months. Five patients, all with signs of blood brain barrier damage, developed transitory mental confusion after ECT. The results indicated that ECT could cause increased dopaminergic activity, which led us to study IV. Single photon emission computed tomography (SPECT) with the cocaine analogue [ $^{123}\text{I}$ ]- $\beta$ -CIT was used in order to visualise dopaminergic neurones in the brain. Six patients with PD were examined before and after a series of ECT, and in three cases SPECT was also repeated after one year. The side-to-side difference in the radiotracer uptake was found to be significantly lower in striatum located contralaterally to the part of the body with most pronounced symptomatology. No significant change in uptake of [ $^{123}\text{I}$ ]- $\beta$ -CIT was seen after ECT, although all patients improved and the most pronounced improvement was seen in patients with less advanced PD.

Study V points at two new positive observations with maintenance ECT (MECT). i.e. repeated ECT treatment of PD. One patient had either severe mental side effects on higher L-dopa doses or intolerable parkinsonian symptoms on lower doses. MECT implied marked improvement in parkinsonian symptoms without mental side effects. Another PD patient, who also had a mental depression, showed slight improvement of motor symptoms on a series of ECT. When treated with MECT further antiparkinsonian effects were seen.

Division of Geriatrics, Department of Neuroscience and Locomotion, Faculty of Health, Linköpings universitet, S-581 85 Linköping, Sweden.

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## LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to by their Roman numerals.

- I P-A Fall, O Axelson, M Fredrikson, G Hansson, B Lindvall, J-E Olsson, and A-K Granéus (1996). Age standardised incidence and prevalence of Parkinson's disease in a Swedish community. *J Clin Epidemiol* 49 (6):637-641
- II P-A Fall, M Fredrikson, Olav Axelson, and A-K Granéus (1999). Nutritional and Occupational Factors Influencing the Risk of Parkinson's disease: A Case-Control Study in Southeastern Sweden. *Movement Disorders* 14 (1):28-37
- III P-A Fall, R Ekman, A-K Granéus, L-H Thorell, and J Wålinder (1995). ECT in Parkinson's disease. Changes in motor symptoms, monoamine metabolites and neuropeptides. *J Neural Transm [P-D Sect]* 10 (2-3):129-40
- IV P-A Fall, S Ekberg A-K Granéus and G Granéus (1999). ECT in Parkinson's disease – dopamine transporter visualised by [<sup>123</sup>I]-β-CIT SPECT .  
Submitted.
- V P-A Fall and A-K Granéus (1999). Maintenance ECT in Parkinson's disease. Accepted for publication after revision. *J Neural Transm*

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## ABBREVIATIONS

[ <sup>123</sup> I]β-CIT	2-β-carbomethoxy-3-β(4-iodophenyl)-tropane
5-HIAA	5-hydroxyindolacetic acid
AVP	arginine vasopressin
BBB	blood brain barrier
CRH	corticotropin releasing hormone
CSF	cerebrospinal fluid
CVI	cerebrovascular incident
DSIP	delta sleep-inducing peptide
ECS	electroconvulsive shock (in animal experiments)
ECT	electroconvulsive therapy
GBS	Gottfries-Bråne-Steen scale (a rating scale for dementia syndromes)
GPi	globus pallidus pars interna
HVA	homovanillic acid
IP	idiopathic Parkinson's disease
LB	Lewy body
MADRS	Montgomery Åsberg Depression Rating Scale
MAO	monoamine oxidase
MECT	maintenance ECT
m-ENK	met-enkephalin
MHPG	3 methoxy-4-hydroxyphenylglucol
MMT	Mini-Mental-Test
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NPY	neuropeptide Y
OR	odds ratio
PCR	polymerase chain reaction
PD	Parkinson's disease
PET	positron emission tomography
SOM	somatostatin
sp	spinal
SP	substance P
SPECT	single photon emission computed tomography
UPDRS	Unified Parkinson Disease Rating Scale

# INTRODUCTION

## ***A historical perspective***

James Parkinson became famous for *An essay on the Shaking Palsy* published in 1817 (Parkinson 1817). He described six cases that formed the basis for his observations. Some observations are still associated with modern definitions of Parkinson's disease. "Involuntary tremulous motion, ... in parts not in action and even when not supported; with a propensity to bend the trunk forward, and to pass from walking to a running pace. .... insidious onset. .... The patient's infirmity gradually increased: the hand failed to answer with exactness to the dictates of the will". He hoped his description would excite others to "extend their researches" to this disease so that they might "point out the most appropriate means of relieving a tedious and most distressing malady." His hope of increasing interest in the disease has been fulfilled as is shown by almost 21000 citations in MEDLINE when "Parkinson's disease" is searched for (1999).

In a historical chapter Tyler describes how such prominent figures in medicine as Trousseau, Romberg and Charcot displayed interest in the disease but were at a loss to define its cause (Tyler 1992). Charcot regarded "palsy" as less relevant in a disease where muscle strength was kept until late stages. "Shaking" was not quite adequate as even advanced disease could occur without tremor. In 1892 Charcot proposed the term "Parkinson's disease".

When it came to therapy, Charcot stated "Everything or almost everything has been tried against the disease". Charcot was one of the first to use hyoscyamine, of which he wrote "...from which some patients have obtained relief; its action, however, is simply palliative."

Important steps forward in therapy have been taken, especially during the past 50 years, and will be mentioned under treatment.

## ***Epidemiology, descriptive.***

Epidemiological studies are of two types, descriptive and analytic. This thesis gives examples of both. Epidemiological investigations of PD are complicated by its very nature.

1. PD is a slowly progressive neurodegenerative disorder with no single identifiable cause. Pathologically, PD is characterised by loss of pigmented neurones and gliosis, most prominently in the substantia nigra pars compacta and locus ceruleus and by the presence of ubiquitin-positive eosinophilic cytoplasmic inclusions in degenerating neurons (Forno 1987). The Lewy bodies (LB) are concentric eosinophilic cytoplasmic intraneuronal inclusions with peripheral halos and dense cores, and their presence is essential for the pathological confirmation of PD. Unfortunately, the LB is not specific to PD (Fearnley and Lees 1997). The diagnosis is clinical, as there is no test which is specific to Parkinson's disease. The clinic diagnostic criteria for PD have varied over time and are not stable and generally recognised. In the present papers our intention was to look for the "essence" of PD as we wanted to find some possible associations between PD occurrence and environmental and occupational factors. Thus we expected to find fewer but more homogenous PD cases. Our criteria for PD, which all had to be fulfilled, have been:
  - History or presence of at least one of the three classical signs - tremor, rigidity and hypokinesia.
  - History of insidious progression.
  - No earlier treatment with neuroleptic drugs.
  - Absence of atypical neurological signs.
  - Positive reduction in classic signs as a result of levodopa treatment in adequate dosage.
2. The diagnosis of PD is based solely on clinical history and examination, which implies an obvious risk of misclassification. A clinico-pathologic study showed clinical over-diagnosis in 18-24 %, depending on which clinical diagnosis criteria were applied (Hughes et al. 1992). Because cases in which the clinical diagnoses are in question are more likely to be referred to autopsy the "real" frequency of over-diagnoses is probably lower. Thus, some cases of atypical parkinsonism may be erroneously diagnosed as PD. Inclusion of these cases in risk factor studies may lead to a diminished chance of finding variables associated with PD.

Different diagnostic criteria and ascertainment of diagnosis may profoundly affect comparisons and study conclusions. So-called “meta-analyses” of PD epidemiological studies with different diagnostic criteria are nearly impossible.

3. The clinical manifestation of PD may be preceded by a long “latent” stage (Koller et al. 1991). The disease process is slow, as shown by the usually long time period from first symptoms to diagnosis. In our paper (No I) this time was assessed as 2.8 years. The finding of Lewy bodies in brains of people not known to have clinical evidence of PD during life is also suggestive of a pre-symptomatic period. “Incidental Lewy bodies” and clinical PD are both age-related phenomena (Tanner, Hubble, and Chan 1996). [<sup>18</sup>F]- PET studies have tried to find pre-symptomatic PD and to measure the rate of progression. The results are not unequivocal but point to different rates of progression in different cases (Brooks 1991; Morrish, Sawle, and Brooks 1995; Morrish, Sawle, and Brooks 1996; Sawle 1993). The possibility of a long latent period makes identification of environmental risk factors difficult.
4. PD is a relatively rare disorder of late life. As a result, even studies comprising relatively large populations will identify relatively few cases, and the potential error in any single study may be significant.

### Incidence and prevalence

Incidence is the most appropriate estimate of disease frequency, as it is the number of cases occurring in a given period in a specific area. It is almost unaffected by disease survival. For a slowly progressive disease such as PD disease survival can affect prevalence. However, measurements of disease incidence are the most difficult, and not many studies in PD have been reported (table 1). The incidence rates in these studies range from 1.5-21/ 100,000- population/ year. In addition to the biologic variation that this interval may represent, it probably reflects variations in study design and case definition. Some researches included postencephalitic Parkinson, “arteriosclerotic parkinsonism” (Gudmunsson 1967), whereas others based the diagnosis solely on medical records and may have included people with other disorders.

Prevalence measures the total number of current cases within a study area. Three methods have been used. The first method is based on case finding in clinical populations, often academic referral centres. The method is associated with selection bias, as social or economic factors may determine who seeks medical care. The second method estimates prevalence

from health service records, and is as subject to biases as the first method, but more diverse clinical populations can be surveyed. In areas where health care is universally available and uniformly delivered without individual economic restraints, good estimates can be obtained using this method. The third method is based on door-to-door screening of a geographically defined population combined with a physician examination of people found in the screening. This is probably the best method but time and expense limits its use. Crude estimates of PD prevalence have been reported to vary from 15/100,000 in 29 provinces in China (Wang et al. 1991) to 669/ 100,000 in a face-to-face screening survey of Junín, Buenos Aires Province, Argentina (Melcon et al. 1997). The last high figure can be questioned both on the grounds of the sampling technique and the relatively small study population( N = 7,765). As might be predicted, and is shown in table 1, the prevalence estimates derived by means of door-to-door methods often are greater than those derived from community-based studies.

**Table 1. Estimated Crude Incidence and Crude Prevalence of Parkinson's disease in some studies.**

Reference	Type of study	Number of cases	Location	Crude Incidence Per 100,000/yr	Crude Prevalence Per 100,000	Age at onset	Age on day of prevalence
(Bharucha et al. 1988)	D	46	Parsi community, Bombay, India		328		
(Li et al. 1985)	D	28	Six cities of the People's Republic of China		44	63.3	
(Melcon et al. 1997)	D (sample)	51	Junin, Buenos Aires, Argentina <sup>1</sup>		399-669 <sup>1</sup>	64	
(Morgante et al. 1992)	D	63	Sicily, Italy		257		
(Schoenberg, Anderson, and Haerer 1985)	D	31	Copiah Couty, Mississippi, USA		347		
(Wang et al. 1991)	D	566	29 provinces, People's Republic of China	1.5	15		
(Ashok et al. 1986)	C	163	Benghazi, Libya	4.5	31		
(Fall et al. 1996)	C	170	Östergötland, Sweden	11	115	65.6	73.7
(Gudmunsson 1967)	C	453	Iceland	16	162	61.1	68
(Kurland 1958)	C	56	Rochester, NY, USA	20	187		
(Marttila and Rinne 1976)	C	484	Turku, Finland	15	120		
(Rajput et al. 1984)	C	138	Rochester, NY, USA	21			
(Sutcliffe and Meara 1995)	C	383	Northampton, UK	12	121		
(Tandberg et al. 1995)	C	245	Rogaland, Norway		111	64.4	73.5
(Wermuth et al. 1997)	C	82	Faroe Islands		187.6	64.2	73.4

C = Community-based study

D = Door-to-Door Surveys

<sup>1</sup> = Different prevalence with 8 different criteria-sets for the diagnosis

### Age-specific distribution

Both the incidence and the prevalence of PD increase with increasing age of the population. PD is rare before the age of 50. The prevalence increases until around the 9<sup>th</sup> decade, when the rates appear to decline (Table 2).

**Table 2. Age-Specific Prevalence of Parkinson’s disease**

Reference	Location	Prevalence (per 100,000) by age groups in years					
		0-39	40-49	50-59	60-69	70-79	80-89
(Fall et al. 1996)	Östergötland, Sweden		19.1	53.4	210.0	614.3	971
(Harada, Nishikawa, and Takahashi 1983)	Yonago, Japan	4.7	39.9	85.5	245.1	698.4	752.7
(Li et al. 1985)	Six cities of the Peoples Republic of China			92.0	145.0	615	>70yr
(Marttila and Rinne 1976)	Turku, Finland	0.8	27.8	136.2	503.5	736.1	468.8 >79yr
(Mayeux et al. 1992)	New York, USA		23	45.7	234.8	525.6	1145 >80yr
(Morgante et al. 1992)	Sicily, Italy		0.0	115.6	621.4	1978.3	3055
(Mutch et al. 1986)	Aberdeen, Scotland		46.6	77.9	254.0	839.6	1925 >79yr
(Okada, Kobayashi, and Tsunematsu 1990)	Izumo, Japan	23.2	19.6	63.6	338.6	478.7	335.7
(Rosati et al. 1980)	Sardinia, Italy	3.3	38.6	204.5	342.1	311.3	82.6
(Sutcliffe and Meara 1995)	Northampton, UK*		6.8	93.3	251	760	1222 >80yr
(Svenson 1991)	Alberta, Canada		46.6	77.9	254.0	839.6	1925 >79yr
(Wang et al. 1994)	Kin-Hu, People’s Republic of China			0.0	780.0	1750	2500 >80yr

\* Mean values are calculated from 5-year groups

The incidence reaches its peak somewhat earlier around the 8<sup>th</sup> decade when most studies show a decline (Fig 2 paper I). By first computing incidence (or prevalence) for different age and sex categories we can then compute a weighted average of the rates with weights from the distribution, traditionally called a *standardised* rate. To make it possible to better compare the occurrence of PD in different populations, with different compositions of ages, an age standardisation can be computed based on another well-defined population. Earlier studies have chosen populations for comparison from defined different dates and regions. Two groups (Tandberg et al. 1995) and ours (Fall et al. 1996) have independently suggested that the “European standard population” constructed for use in cancer epidemiology be used even here. If this becomes the future standard procedure, it will make comparisons between studies easier.

**Epidemiology, analytic**

There are many factors that have been associated with altered risk of PD. (Table 3)  
 Demographic factors such as age, male gender and race (white) appear to increase the risk of developing PD. All studies find age associated to an increased risk, and this could be interpreted as an age-related neuronal vulnerability.

**Table 3. Factors Associated with Altered Risk of Parkinson’s disease**

<b>Increased risk</b>	<b>Decreased risk</b>
Ageing, gender (men), race (Caucasian)	
Diet Sweet foods Snacks	Diet Vitamin E, supplemental multivitamins Cod liver oil Tocopherol Vegetables Fruit Fried or broiled meat, smoked ham or meat, French loaf or white bread, tomatoes. *
Family history of PD	
Life experience: Trauma. Emotional stress. Personality (shyness and depressiveness)	Life experience Cigarette smoking Drinking alcohol Coffee*
Environmental exposures Metals (manganese, iron) Drinking well water Farming Rural residence Wood pulp mills Steel alloy industries Herbicide and pesticide exposure MPTP and MPTP-like compounds Female cleaners*	Environmental exposure Drivers* Metal workers*
Infectious agents	

\* Paper II in this thesis

Men appear to have a slightly (about 1.5 times) higher risk of acquiring PD than women (Fall et al. 1996; Marttila 1992). Results of studies on different risks for different races are controversial due to questionable study designs. Some studies suggest that African Blacks and Asians may have a lower occurrence of PD than Caucasians (Kessler 1972; Kurtzke and Murphy 1990; Lilienfeld et al. 1990). However, the differences may reflect different socio-

economic factors that influence e.g. life expectancy and thus the risk of acquiring PD. These, in turn, influence the possibility of consulting a doctor and therefore the possibility of being diagnosed. A door-to-door study in Mississippi indicated similar prevalences for Blacks and Whites (Schoenberg, Anderson, and Haerer 1985).

After the tragedy with pyridine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which induced PD-like disease in young people (Langston, Ballard, and Tetrad 1983) the interest in an environmental cause of PD increased. Studies seeking an association between environmental exposure and PD have suggested an increased risk associated with farming, rural residence, herbicide/ pesticide exposure, iron or mining, steel manufacture and employment in industries manufacturing chemicals, and wood pulp and paper (Aquilonius and Hartvig 1986; Barbeau et al. 1987; Fall et al. 1999; Golbe, Farrell, and Davies 1990; Hertzman et al. 1990; Ho, Woo, and Lee 1989; Hubble et al. 1993a; Koller, Vetere-Overfield, and Gray 1990; Rajput et al. 1986; Semchuk, Love, and Lee 1992; Tanner, Chen, and Wang 1989; Tanner, Grabler, and Goetz 1990). Many of the exposures mentioned are of non-specific nature. Table 4 shows some risk factors for PD based on case-control studies. Some other risk factors have been proposed such as trauma, infection, and premorbid personality. These will not be mentioned further in this review. Besides increasing age, the strongest risk factor associated with PD is the presence of the disease in a family member. Most reports suggest either an autosomal-dominant inheritance with a variable penetrance or a multifactorial causation. . Three different genes have been mapped for different rare familial Parkinsonian syndromes. At present, there is no evidence that any of these genes for familial Parkinsonian syndromes have a direct role in the aetiology of the common sporadic form of PD (Gasser 1998). The manifold putative causative factors are often supposed to act on genetically susceptible individuals. We are just preparing a manuscript on analyses of genotypes of glutathione S-transferases and microsomal epoxide hydrolase with PCR –assay in PD patients and controls. Our observation suggests that impaired ability to detoxify reactive metabolites may increase the individual susceptibility to toxicity induced by both endogenous and exogenous compounds (Ahmadi et al. 1999).



## **Treatment**

The best-known strategies in the management of PD can be summarised as pharmacological, surgical, paramedical, and life-style connected approaches such as exercise, education, support, and nutrition.

### Pharmacologic

**Levodopa** is the most effective drug in the treatment of PD. Treatment is associated with decreased morbidity and mortality, and almost all patients benefit from treatment (Olanow and Koller 1998). In modern therapy levodopa is routinely administered in combination with decarboxylase inhibitor to prevent the peripheral conversion of levodopa to dopamine with resultant side effects. After five years of therapy, 75% of patients have either developed troublesome response fluctuations (“wearing off” and “on-off” phenomena) or dyskinesias (Fahn 1992; Granéus 1978). During the wearing-off, dose failures, and on-off states there is disability with pronounced parkinsonian symptoms and signs, leaving patients immobile with akinesia for long hours at a time. Sometimes during the akinetic periods the patients have painful sustained contractions, called “off” dystonia. Dyskinesias (abnormal involuntary movements) are usually choreic in nature and often show a temporal correlation with peak plasma levodopa levels (Eriksson et al. 1984). The mechanisms behind levodopa-related complications are poorly understood. The short plasma half-life of levodopa is a contributing factor since continuous administration by intravenous or intraduodenal infusions lessens fluctuations (Nilsson et al. 1998). The treatment of levodopa-related motor complications has remained largely unsuccessful. Neuropsychiatric problems occur in at least one-third of PD patients and can be even more disabling than motor dysfunction. Some mental symptoms, such as cognitive dysfunction and depression, can be part of the disease process. The antiparkinsonian medication involves an increased risk of acquiring confusion and hallucination.

**Dopamine agonists** share the capacity to directly stimulate dopamine receptors. In Sweden bromocriptine, cabergoline, ropinirole and pramipexol are now available. They offer some theoretical advantages to levodopa. First, they do not require metabolic conversion to an active product and thus are not dependent in the same way as levodopa on degenerating

dopaminergic neurons. Second, most dopamine agonists have a longer duration of response than immediate-release formulations of levodopa, therefore an individual dose can provide a more sustained stimulation of the dopamine receptor. Third, agonists do not undergo oxidative metabolism and therefore do not generate free radicals that can be harmful to the living cells.

**COMT inhibitors** inhibit the ubiquitous enzyme catechol-O-methyltransferase in the periphery, thus more levodopa is available to cross the blood brain barrier (BBB). COMT-inhibitors should be combined with levodopa.

**Anticholinergics** are the oldest drugs in the treatment of PD but adverse effects are common and often limit their use.

**Amantadine** is an antiviral agent discovered by chance to have an antiparkinson effect. Amantadine has been reported to be more effective than anticholinergic drugs regarding akinesia and rigidity but less effective with regard to tremor. Important side effects such as confusion, hallucinations, insomnia and nightmares limit its use.

**Selegiline**, a selective monoamine oxidase (MAO)-B inhibitor, was marketed as a neuroprotective drug, but analyses have shown that selegiline can induce symptomatic effects that might account for all or part of the benefits observed (The-Parkinson-study-group 1993). The drug protects motor neurons from toxicity in some in vitro and in vivo laboratory studies. One study reports increased mortality in patients receiving selegiline (Lees 1995). That study, however, has been criticised for methodological and statistical flaws, and the future will show the place of selegiline in the therapy of PD.

## Surgical

**Thalamotomy** was for many years the method of choice for stereotaxic surgery in PD. It was effective for tremor, rigidity, and levodopa-induced dyskinesia but ineffective for akinesia and sometimes it worsened gait or speech disorders.

**Pallidotomy** has been tried since the 1950s but the first series with good result was operated by Leksell (Svennilsson et al. 1960). The method was favourably reexplored by Laitinen et al. (Laitinen, Bergenheim, and Hariz 1992). The lesions were placed in the posteroventral portion of globus pallidus pars interna (GPi) and Laitinen reported a significant improvement in parkinsonian motor signs and on levodopa-induced dyskinesia. Several centres have reported amelioration of parkinsonian motor signs after stereotaxic pallidotomy. Results are, however, not uniformly successful across centres.

**Chronic deep-brain stimulation** is a new promising technique, and reports from different target areas in the brain are appearing. For overviews of different stereotaxic and deep brain stimulation methods in PD see Benabid and Vitek (Benabid et al. 1998; Vitek 1996).

**Fetal nigral transplantation** has been performed in more than 150 cases, and results are inconsistent. Lindvall et al in a Swedish group have been early in this field (Lindvall and Bjorklund 1989; Lindvall et al. 1989). In a review of six published works with a total of 21 patients, 4 patients showed marked benefit and 8 moderate benefit (Olanow, Freeman, and Kordower 1996). In a few cases cellular survival is demonstrated with PET. Regarding the costs, the difficulty of obtaining donor cells, the small fraction of donor cells that survive, and the varying outcome of transplantation, the method needs further refining and evaluation.

## ECT

**The mechanisms of the anti-parkinsonian effect of ECT** are only partly understood. An increased dopaminergic activity after electroconvulsive shock (ECS) was postulated by Modigh (Modigh 1975) because of an enhanced psychomotor stimulant effect of clonidine and/or apomorphine in dopamine depleted mice. In an autoradiographic study in rats, Barkai et al (Barkai, Durkin, and Nelson 1990) were able to demonstrate an induced upregulation of D1 receptors in many brain regions, including substantia nigra after repeated ECS. Later a more than tenfold increase of DA was found in striatum in rats during the course of electroconvulsive shock (ECS) when interstitial concentrations of DA were measured by microdialysis (Nomikos et al. 1991). In man Bolwig et al. found an increased permeability of the BBB for small hydrophilic tracers during ECT, and have suggested that the increased effects of dopamine agonists seen in animal studies are related to disruption of the BBB

permitting an increased dopamine access to the CNS sites (Bolwig, Hertz, and Holm-Jensen 1977). The increase of HVA in cerebrospinal fluid (CSF) after ECT in patients with PD has been interpreted as an indication of increased dopaminergic activity (Fall et al. 1995). Olson and colleagues have shown an upregulation of glial cell derived neurotrophic factor (GDNF) mRNA in striatum and cortical areas after induced status epilepticus in rats (Schmidt-Kastner et al. 1994). If there is a similar effect on GDNF in man after ECT it might explain some of the longstanding effects of ECT.

**Reports on ECT in the literature.** Starting with the observation by Kalinowsky who described improvement in both parkinsonian symptoms of 7 year's duration and depression in a 68 year-old woman, a considerable number of reports on this subject have been published (Kalinowsky 1949). A MEDLINE search on the terms ECT and Parkinson's disease gave 109 references in English. Some further reports were found via the search motor ALTA VISTA. Further references were found from the thus generated reference lists. I have found 48 reports on ECT in PD, of which 24 are case reports with 29 patients included (Ananth, Samra, and Kolivakis 1979; Asnis 1977; Atre-Vaidya and Jampala 1988; Barcia and Martinez Pardo 1978; Berger and de Soto 1990; Burke, Peterson, and Rubin 1988; Dam, Pakkenberg, and Bolwig 1992; Dysken et al. 1976; Fall and Granérus 1999b; Gallinek 1947; Hermesh et al. 1992; Holcomb, Sternberg, and Heninger 1983; Hurwitz, Calne, and Waterman 1988; Jaeckle and Dilsaver 1986; Kalinowsky 1949; Lebebohn and Jenkins 1975; Levy, Savit, and Hodes 1983; Lipper and Bermanzohn 1975; Rainey and et al. 1975; Stern et al. 1991; Ward et al. 1980; Wilder, Brown, and Lebensohn 1975; Young, Alexopoulos, and Shamoian 1985; Yudofsky 1979). Twenty-three papers report improvement in PD-symptoms and only one (Gallinek 1947) describes unchanged PD symptoms. Of the 16 cases where duration of improvement was noticed, 12 had a duration from 6 weeks to > 3 years. Nineteen case reports deal with depression and PD. Four reports are about psychosis and PD. One case report describes a patient with merely PD.

**Maintenance ECT (MECT).** In most of the existing literature, ECT was given as a single course of treatments. Very little information is available on ECT given as single sessions at different intervals after an initial series of ECT sessions. We have found five reports with a total of twelve patients given MECT (Aarsland et al. 1997; Holcomb, Sternberg, and Heninger 1983; Serby et al. 1994; Wengel et al. 1998; Zervas and Fink 1991). Eight patients

showed a definite improvement in Parkinsonian symptoms and were treated between three months and four years. Three of the twelve patients had, however, increased dyskinesias.

Tables 5 A and 5 B show case series or prospective studies and reviews, respectively. Table 5 A shows 24 case series or prospective studies including 180 patients, with one (Andersen et al. 1987) controlled, prospective, and double blinded. Twenty-two reports describe improvement in PD-symptoms with duration from a few days to eight years.

Table 5 B shows 15 reviews at least partly dealing with ECT as treatment of PD.

**Table 5 A. Reports on ECT effects on PD. Modified and enlarged after Faber (Faber and Trimble 1991). Case series or prospective studies.**

Study	No. Of pts	Patient history	ECT	Results on PD	Response duration
(Fromm 1959)	8	PD without psychiatric co-morbidity		5 pts with rigidity and bradykinesia; noticeable remissions. 3 pts with tremor-dominant PD; no response	2-3mths
(Brown 1975)	7	M age 67. All moderately to severely demented	1-4 series, 8 sessions per series	No comment on PD symptoms ("poorer than usual" antidepressant effect)	NS
(Balldin et al. 1980)	(5)	PD No psychiatric diagnosis	4-8 sessions	Detailed ratings. All improved. Two dramatically. Included in (Balldin et al. 1981)	A couple of days to 4 mths
(Ward et al. 1980)	5	PD with "on-off" syndrome Age M = 57 On-off $\geq$ 1 yr	6 sessions bilat	Mild subjective improvement of short duration in 2 pts. Self-scoring and clinical observation. In discussion 1 pat with depr + PD was given 3 series of ECT with dramatic but short-term effect.	No significant change.
(Balldin et al. 1981)	9	PD with "on-off" PD 6-20 yrs Age M = 62	3-8 sessions	Detailed ratings used. 5 marked improvement, 2 slight improvement, 2 no change	2-41 w
(Balldin et al. 1982)	(9)	Same as (Balldin et al. 1981)		ECT increases responsiveness of dopamine receptors	-
(Baruch et al. 1985)	6	M age 67 Major depr	7-15 sessions	4 of 6 improved. None of the 4 responding pts needed anti-parkinsonian medication at follow-up	3-8 yr
(Andersen et al. 1987)	11	M 70 yr old. M 15 yr PD "on-off" Not depressed	5-6 sessions 6 pts initially on sham ECT switched to real	No change with sham, 9-11 improved with real ECT Double blinded controlled, prospective study.	2-6 w
(Douyon et al. 1989)	7	M 67 yr PD m = 9 yr Depr	M 7 sessions bilat	All 5 aspects (i.e. rigidity, tremor, bradykinesia, gait, and postural stability) improved. Rating scales used. All improved and older showed greatest improvement	NS
Continued....					

Continued					
Study	No. Of pts	Patient history	ECT	Results on PD	Response duration
(Goswami et al. 1989)	9	Schiz with neuroleptic induced Pm	9 bilat	Prospective, longitudinal triphasic design: neuroleptics – neuroleptics plus ECT – neuroleptics. “ECT has a true antiparkinsonian potential”. Weekly ratings during ECT series and 2 weeks after. Rating scales used	Only followed for 2 w
(Zervas and Fink 1991)	4	69-75 yr old medication refractory PD 5-18 yr H&Y 4-5	8-12	All had measurable improvement in rigidity, tremor, bradykinesia and on-off. Rating scales used. Full doses of dopamine agonists and ECT were followed by increased cognitive impairment. In 2 patients with reduced dopa-agonist dose no signs of organic mental syndrome.	2 pts had MECT for 3 and 6 mth All reverted to pre-treatment level after 3-6 w after last ECT
(Birkett 1991)	5	M 76 yr old Depr And PD	3-9 unilat	Rating scales used. 3 pts effect on depr + PD. 1 pat only on PD, 1 pat only on depr.	1 > 2 yr 2 > 2 mth 1 < 1 mth
(Figiel et al. 1991)	7	M 66 yr old PD m = 3.3 yr Depr	No NS 4 pat bilat 3 pat unilat	5 showed some improvement in PD-signs. Delirium seen 7-21 days after last ECT in all 7 cases	NS
(Figiel 1992)	20 depr + PD 20 CVI + PD	NS	NS	ECT effective both on depr and PD symptoms. Depr + PD group delirium 85% Depr + CVI group delirium 25%	NS
(Oh et al. 1992)	11	M 70 yr old PD m = 5.5 yr 10 depr, 1 bipolar disorder	3-9 sessions m = 5..9 9 unilat 2 bilat	Movement symptoms improved in 2. Relief in psychiatric symptoms in 9 Post-ECT delirium in 7 pts	< 6 w
(Aarsland, Larsen, and Tandberg 1993)	3	59-74 yr old Pm + depr (1 MSA, 1 MSA/NI, 1 PD)	6-12 unilat	Rating scales used. All markedly improved.	1 pt > 5 mth 1 pt 3 w 1 pt > 3 w
(Serby et al. 1994)	3	PD	6-8 initial series MECT each 4-6 Weeks intervals	Improved “on” scores. Prolonged “on”-time. Sustained benefit in 2 pts. Two had transient exacerbations of dyskinesias.	Followed 1 yr
Continued...					

Continued					
Study	No. Of pts	Patient history	ECT	Results on PD	Response duration
(Fall et al. 1995)	16	Non-depr Nondement	4-9 sessions M= 7 Unilat	Significant improvement in Webster, walking speed, motor subscale of GBS	1 –18 mth 7 – 3-5 mth 8 – 2 days-4 ws
(Pridmore, Yeo, and Pasha 1995)	15 but only 10 for assessment		4 sessions unilat	Scales were used before, immediately after and 2w after ECT. Significant improvements for akinesia, tremor, rigidity, feeding, speech, H&Y. Psychiatric monitoring showed no serious side effects. 4 showed transient confusion. No systematic follow up	Some > 16w
(Pridmore et al. 1996) Follow-up of same pts as above	(12)			No correlation between neuro-psychologic and physical responses. Improvement in long-term storage and behavioural memory. Greater cognitive gains by younger subjects.	Neuro-psychiatric testing before and 2 w after ECT
(Aarsland et al. 1997)	2	Both 63 yr old Case 1/ PD 6 yr H&Y 5	Case 1: 12 unilat + 33mth MECT (57ECT) Case 2/ 6 unilat +4 yrs MECT (53ECT)	Case 1: H&Y from 5 to 1.5 neuropsychological assessments. Case 2: H&Y from 5 to 3. Off-time from 50 to 10% of total time. From confined to bed to independent of help.	Case 1 : 12 and 10w after ECT series. With MECT > 3yr Case 2: 4mth, 14 mth after ECT series. With MECT > 4yr
(Wengel et al. 1998)	4	Nondepressed Nondemented	I +MECT every 3-4 w for 12 mths Bilat	2 had reduction in “off” time without impairment of cognitive functioning 1 developed cognitive impairment after 7 MECT. 1 showed delusions during the acute phase	Up to 12 mth
(Moellentine et al. 1998)	25	M 71 yr old PD + Depr (25) (control group with 25 only psychiatric)	Most unilat	The PD group: 14 improved, 10 unchanged 1 deteriorated Rating scales used	NS
(Fall et al. 1999a)	6	M 74 yr old 5 PD 1 PD + depr	6 sessions unilat	Scales used. Statistically improvement in ADL and motor scales.	1-17 mth (4 > 3mth)

bilat = bilateral  
 CVI = cerebrovascular incident  
 depr = depression  
 GBS = Gottfries, Bråne, Steen rating scale  
 H&Y = Hoehn and Yahr rating scale  
 I = Inital series of ECT  
 M = mean  
 MECT = maintenance ECT  
 MSA = multiple system atrophy  
 mth = month  
 NI = neuroleptic-induced  
 NS = not specified  
 Pm = parkinsonism  
 Pt = patient  
 Schiz = schizophrenia  
 TD = tardive dyskinesia  
 unilat = unilateral  
 w = week  
 yr = year

**Table 5 C. Reviews and editorials dealing with ECT and effects on PD.**

<b>Study</b>	<b>Notes</b>
(Yudofsky 1981)	Review of ECT in general hospitals and drug-refractory PD is mentioned
(Major 1984)	Review of ECT. ECT mentioned
(Abrams 1989)	Editorial, review. Recommends therapeutic ECT in intractable and drug-resistant PD.
(Emery 1996)	ECT for Parkinson's disease. 36 references
(Faber and Trimble 1991)	ECT in PD and other movement disorders. 94 references
(Rasmussen and Abrams 1991)	Review and recommendations for current practice. 31 references
(Dam, Pakkenberg, and Bolwig 1992)	Review of ECT in PD and discussion of possible pathophysiological mechanisms of action
(Kapur and Mann 1992)	Review of "Role of the dopaminergic system in depression" Discussion on effects of ECT in PD-pts
(Kapur and Mann 1993)	"Antidepressant action and the neurobiologic effects of ECT: Human studies."
(Cummings 1992)	"Depression and Parkinson's disease: A review"
(Kellner et al. 1994)	"Electroconvulsive Therapy and Parkinson's Disease: The case for Further Study"
(Marsden 1994)	Review of PD. A few positive lines on ECT as treatment.
(Emery 1996)	Review. "ECT for Parkinson's disease. Reconsidering an old concept."
(Young, Camicioli, and Ganzini 1997)	Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. ECT mentioned.
(Irvin 1997)	Review of "Treatment of depression with outpatient electroconvulsive therapy". Points to outpatient treatment also in PD.

The literature reviewed is more notable for its quantity than its quality, but I conclude that approximately half of the patients with severe PD might be expected to have a meaningful clinical response of sufficient duration to make ECT a worthwhile consideration when current therapies are unsatisfactory.

## THE AIMS OF THE WORK

The aims of this thesis were:

- To assess the occurrence of PD in the Central Health Care district of the county of Östergötland, Sweden, where a low drug utilisation suggested a low prevalence of PD. We also wanted to introduce the use of the European Standard Population as a tool for easy comparisons of PD prevalence between different areas and time periods (I)
- to investigate the possible impact of some nutritional and environmental risk factors for Idiopathic Parkinson's disease in a case-control study (II)
- to estimate the frequency of patients showing an antiparkinsonian response to ECT, the duration of the antiparkinsonian effect and to look for biochemical and clinical predictors of a long-term antiparkinsonian effect (III)
- to study the possible effect of ECT on dopamine transporter studied with [ $^{123}\text{I}$ ] $\beta$ -CIT SPECT, to evaluate whether [ $^{123}\text{I}$ ] $\beta$ -CIT uptake can be of any value as a predictor of the effects on PD, and to study the effect of ECT on some less advanced PD cases than reported before (IV)
- to report on the observation of two effects of maintenance ECT in PD;  
1/ antiparkinsonian effect without levodopa provoked paranoid delusions and  
2/ improvement in PD motor and cognitive symptoms in excess of conventional series of ECT (V)

## SUBJECTS AND METHODS

### *Epidemiological section*

The county of Östergötland has almost 400,000 inhabitants and is divided into catchment areas of four hospitals. There are no private hospitals that take care of PD in the area. The population under investigation comprised the inhabitants in the Central Health Care District in Östergötland with a population of 144,777 in December 31, 1989. The population of the area is almost entirely Caucasian. The area had one city, Linköping, with a population at that time of 120,544. The day of prevalence was taken to be August 31, 1989.

### Patients and controls paper I

At the time of the study all antiparkinsonian medication was free of charge provided a doctor had given a prescription. Each visit to pharmacy allows medication for a maximum of three months to be dispensed. The prescription form gives the identification of the patients (National registration number), the reason for the prescription, the prescribed drug, and the dosage. We collected all antiparkinsonian prescriptions at the pharmacies during six months. The public medical service is well supplied in the area and there are good reasons to believe that most PD patients with a certain degree of symptoms and at least those on medication were found. The Ethical Committee of the Faculty of Health Sciences, Linköping University, The Swedish Data Inspection Board and the National Board of Health and Welfare, Department of Drugs have approved the study. To further improve case finding we scrutinised the files at the neurological and the geriatric departments for PD patients. We also asked all doctors in the neurological and geriatric departments, as well as all general practitioners and nursing homes, in the region to report all PD patients under their care.

### **Assessing the diagnosis of PD**

The method described gave 340 patients treated with antiparkinsonian drugs. From the information on the prescriptions 135 patients were withdrawn as obviously not having PD. The majority of this group suffered from drug-induced parkinsonism (n= 109), but there were a few cases of lactation inhibition, treatment of restless legs and pituitary tumours. Of the

remaining 205 patients 74 were found to have been examined previously by specialists within the geriatric or neurological clinics, and their diagnoses were settled by scrutinising their records.

A senior neurologist (GH) personally examined one hundred and thirty subjects. For one patient no data except the prescription could be found. For PD diagnosis we used the criteria already described under Introduction/ Epidemiology/Descriptive. We also used two further diagnostic groups Possible Parkinson’s disease and Parkinsonism plus syndromes (see paper I, methods). We found 170 PD all together, see table 6.

**Table 6. Specification of different diagnostic groups**

<b>Patient group</b>	<b>n</b>	<b>per cent</b>
Parkinson's disease	170	82.9
Parkinsonism plus syndromes	13	6.3
Post-traumatic parkinsonism	1	0.5
Possible Parkinson's disease	1	0.5
Other diagnoses	19	9.3
Drug-induced parkinsonism (9)		
Essential tremor (3)		
Restless legs (3)		
Buccolingual syndrome (1)		
Cerebrovascular disease (1)		
Rigidity unspecified (1)		
Non-Parkinson’s disease unspecified (1)		
No file available	1	0.5
<b>Total</b>	<b>205</b>	<b>100</b>

**Prevalence and incidence**

To make it easier to compare prevalence and incidence from different populations with divergent age compositions we suggest using a theoretic standard population originally introduced in cancer research (Doll 1976). The composition of the European Standard Population and an example of the calculation are given in table 7.

## Patients and controls paper II

In paper II we used a questionnaire that contained a set of questions that have been used in several earlier epidemiological studies and covered 222 variables (Arbman et al. 1993) (for details see paper II). It contained a food frequency list with questions covering the previous 15 years and included a food list of 29 items as well as smoking habits and alcohol consumption. The questionnaire also contained questions about occupational history and time spent in different jobs. All jobs that the patient and the control subject had held during their lifetime up to the year of answering the questionnaire were listed. Of the 170 PD patients from paper I we restricted the patients under study to those between 40 and 75 years of age. This was in order to achieve agreement with the control group and minimise the risk of recall bias due to poor memory among the respondents. Fourteen of the patients did not answer the questionnaire despite two written reminders and telephone calls to the patients or proxies when the patients seemed unable to answer properly. Another eleven patients were omitted, as onset of IP was not given. Thus 113 cases remained for analysis. The mean duration of the disease – from onset to day of prevalence – was  $8.3 \pm 6.3$  years ( $M \pm SD$ ).

The control group was randomly drawn from the Regional Population Register of the County of Östergötland. This group originally comprised 600 people aged 40-75, who in 1985 received the questionnaires by mail, together with an introductory letter. The controls in this study were restricted to the 321 who lived within the Central Health Care District. If there was no reply after two written reminders, the controls were called by telephone to complete the questionnaire. Fifty-eight controls did not answer the questionnaire, and the response rates for the cases and the controls were 89.8% and 81.9 %, respectively.

The patients were aged  $62.9 \pm 8.9$  years and the control subjects  $56.8 \pm 10$  years on average ( $M \pm SD$ ), a difference taken care of in the stratified as well as the multivariate analyses. For reasons of comparability between cases and controls regarding duration of exposure, the exposure was assessed until onset of disease and not thereafter. “Age” for controls was age on answering the questionnaire whereas “age” for the patients is age at onset of IP.

## **ECT section**

### **Paper III**

Sixteen non-depressed, non-demented patients with advanced PD and unsatisfactory PD treatment were included in a prospective study. The patients were  $70.3 \pm 5.1$  years old and their disease had a duration of  $16.9 \pm 8.6$  years ( $M \pm SD$ ). The Hoehn and Yahr clinical state was  $3.6 \pm 0.6$  and the Webster score during the best part of the day,  $15 \pm 3.4$  (Hoehn and Yahr 1967; Webster 1968). Before ECT the full Gottfries-Bråne-Steen scale (GBS) (Gottfries et al. 1982) was used among other things to exclude dementia, and the Montgomery-Åsberg-Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979) was applied to exclude mental depression. The study was approved by the Ethical Committee of the Faculty of Health Sciences and the patients had given their informed consent.

### **Clinical parameters checked before, after, and at follow up:**

Webster score

Time to walk 10 m

Number of steps to walk 10 m

Motor subscale of GBS

### **ECT procedure**

Unilateral ECT on the non-dominant hemisphere was given to all patients but two, with motor seizures less than 30 sec, who received bilateral stimulation in one and five subsequent sessions, respectively. Details of premedication and anaesthesia are given in paper III. We used a Siemens convulsator 622 with unidirectional square-wave pulses.

### **Lumbar puncture**

The lumbar puncture was performed at 8 a.m. after an overnight fast when the patients had been confined to bed. No drugs were given later than 11 p.m. the preceding night. The lumbar puncture was performed with the patient in his own bed in the recumbent position. Most punctures were performed at the L4-5 level and at the L3-4 level only when no CSF was obtained at the first level. A 0.7mm Yale Spinal needle was used. Sixteen ml cerebrospinal fluid was collected in two 12 ml test tubes with 11 and 5 ml respectively. The CSF in tube 1 was well mixed and immediately put into ice water. It was centrifuged at 4° C.

1,500 x g for 15 minutes, decanted and divided into ten test tubes according to a fixed routine with the same tube number analysed for the same substance. The portions varied depending on requests from the laboratories from 0.5 to 2 ml and were stored within 1 hour at -80° C until assayed. Time was noted when CSF sampling was finished. The CSF in tube 2 was not centrifuged but sent within 30 minutes to our laboratory for analysis of cells and albumin. We analysed the concentrations of homovanillic acid (HVA), 3-methoxy-4-hydroxy-phenylglucol (MHPG), and 5-hydroxyindoleacetic acid (5-HIAA), which are metabolites of dopamine, norepinephrine and serotonin, respectively. We also analysed the concentrations of six neuropeptides specified in paper III.

#### Paper IV

We chose to treat six PD-patients with different degrees of disease severity – see paper IV table 3. Two of the patients showed some depressive symptoms on the MADRS. Staging according to Hoehn and Yahr was performed before ECT treatment. Before and after the ECT series we checked the Mini Mental Test (MMT) (Folstein, Folstein, and McHugh 1975). Lumbar puncture was performed, and analyses were made for sp/s albumin ratio and monoamine metabolites.

#### **Clinical parameters checked before and after ECT:**

Unified Parkinson's Disease Rating scale (UPDRS) (Fahn, Elton, and Committee 1987).  
Webster, scale for degree of disability (Webster 1968).  
Percent registered time of day with "normal movements".

#### **ECT procedure**

Details of premedication and anaesthesia are given in paper IV. Unilateral ECT on the non-dominant hemisphere was used. The delivered mean charge was  $212 \pm 91$  (M  $\pm$  SD) mC and the duration of cramps on electroencephalograph (EEG) was  $52 \pm 14$  (M  $\pm$  SD) s. We used a Thymatron TM DGx delivering bipolar brief Pulse Square waves.

#### **SPECT**

[<sup>123</sup>I]β-CIT was purchased from MAP Medical Technologies OY, Tikkakoski, Finland. The patients were injected intravenously with a mean dose of 130 MBq diluted in about 3ml of

saline. SPECT imaging was performed 20 hours after injection of tracer using a single head rotating gamma camera (GE XRT, Starcam 3000). For details see paper IV.

## Paper V

Two patients, one from each of the studies in papers III and IV, were given maintenance ECT (MECT). They were regularly checked at out-clinic visits with the same tests as in the papers mentioned and one of the patients made daily recordings of “on”-time.

## STATISTICS

More detailed information on the statistics used are given in the separate papers. In the epidemiological section the basic analyses were stratified by age and gender, and the odds ratio was used as a measure of relative risk. All factors associated with increased risk in the univariate analyses were included in several multivariate logistic regression analyses. In the ECT section, as a main rule, statistical methods such as Student’s t-test and Pearson product-moment correlation coefficient were applied when interval or ratio scales were used. In the case of lower scale levels, non-parametric methods were used such as the Spearman rank correlation coefficient in correlation analyses. For correlated data the paired Student’s t test and the Wilcoxon signed rank test were used. The normal Student’s t test and Mann-Whitney U test were used for uncorrelated data. The other methods used was Fisher’s exact probability test for small-sample categorical data.

## RESULTS

### *Paper I*

Paper I deals with descriptive epidemiological data. Crude prevalence for ID, with our “rather strict” definition was 115 per 100,000 people. Standardised for age using the European Standard Population, the corresponding figure was 75.7. See table 7.

**Table 7. Computation of age-standardised prevalence rates using European Standard Population. (Doll 1976). PD in the Central Health Care District in Östergötland.**

Age in years	Cases n =	Population under Investigation	Observed prevalence	No. of People in European Standard Population	Expected cases in European Standard Population <sup>1</sup>
0-4	0		0	8000	0
5-9	0		0	7000	0
10-14	0		0	7000	0
15-19	0		0	7000	0
20-24	0		0	7000	0
25-29	0		0	7000	0
30-34	0		0	7000	0
35-39	1	9,963	10.0	7000	0.7
40-44	1	11,027	9.1	7000	0.6
45-49	3	9,623	31.2	7000	2.2
50-54	1	7,829	12.8	7000	0.8
55-59	7	7,144	98.0	6000	5.9
60-64	11	7,405	148.6	5000	7.4
65-69	21	7,480	267.9	4000	10.7
70-74	39	6,491	600.8	3000	18.0
75-79	34	5,393	630.5	2000	12.6
80-84	38	3,552	1070.0	1000	10.7
85+	14	2,296	609.8	1000	6.1
<b>TOTAL</b>	<b>170</b>	<b>147,777</b>	<b>115</b>	<b>100,000</b>	<b>75.7<sup>2</sup></b>

<sup>1</sup> Expected cases in European Standard Population in each age group =  
Observed prevalence · number of people in European Standard Population for the same age group.

<sup>2</sup> Total = sum of expected cases in this column.

Crude Incidence was 11 per 100,000 person-years. The age-specific prevalence increased up to the age groups 80-84 in which it was 1070 per 100,000. With higher ages, the prevalence decreased. The age-specific annual incidence was from 1.6 in the lowest to 79.5 per 100,000 in the highest age groups. The mean age at onset of the disease was 65.6 and the mean age on the day of prevalence assessment was 73.7. The male-to-female ratio was 1.5.

## **Paper II**

In this paper nutritional and occupational factors influencing the risk of Parkinson's disease were studied. No food item was associated with a statistically increased risk of contracting IP. A reduced risk was found for fried or broiled meat, smoked ham or eggs, French loaf or white bread, and tomatoes. Reduced risks were also seen for coffee, beer, wines, and spirits. Spirits were also adjusted for male gender and smoking and there was still a reduced risk. A preventive effect of smoking was shown (OR = 0.17) and remained after adjusting for male gender and spirits.

When the genders were analysed separately, a significantly increased risk of IP was found for male carpenters (OR = 3.9) and for female cleaners (OR = 6.7). Males handling pesticides in any occupation had an increased risk with OR = 2.8 with a two-tailed *p*-value of 0.08 but a one-tailed *p*-value of 0.04. (The hypothesis of an increased risk in the case of pesticides and PD is clearly in one direction.)

Smoking and various alcoholic drinks were included in a multivariate logistic regression analysis, together with all the factors in Tables 1 through 3 in paper II. Odds ratios below unity were obtained for smoking in seven models. When adjusted for smoking and spirits, odds ratios for almost all food factors in all models remained below unity but with a confidence interval including unity, except coffee >5 cups a day.

Multivariate analyses still showed increased risks for male carpenters (OR = 4.3), male cabinet-makers (OR = 3.2), and female cleaners (OR = 8.9). In a model including those determinants of risk for men that seemed most pertinent, that is, smoking, spirits (three categories), fried or broiled meat (two categories), coffee (two categories), carpenters, cabinet-makers, and handling pesticides in any occupation, the overall pattern from the stratified analyses remained, except for fried and broiled meat daily. Significant or almost significant odds ratios were found for handling pesticides in any occupation (OR = 3.3, CI 1.0-10), smoking (OR = 0.26, 95CI 0.07-0.89), and coffee >5 cups a day (OR = 0.14, 95% CI 0.03-0.60).

### **Paper III, IV and V**

All 16 patients in paper III and all 6 in paper IV showed improvement of motor symptoms after a series of ECT. In paper III the most obvious changes were seen in gait ( $p = 0.002$ ), upper extremity swing ( $p = 0.005$ ), rigidity ( $p = 0.006$ ), and tremor ( $p = 0.003$ ). The positive motor response was usually seen after the second or third ECT-session. The monoamine metabolites HVA and the neuropeptide NPY in CSF increased significantly after ECT.

We divided the patients into two groups, one with long- and one with short-term effect. The levels of MHPG in CSF before ECT were significantly lower in the group with long-term effect but there was an overlap between the two groups. In papers III and IV, patients with less pronounced disease showed the longest effect duration. We also found that patients with a high sp/s albumin ratio, indicating a BBB damage (Link and Tibbling 1977; Tibbling, Link, and Öhman 1977), have a high risk of mental confusion in connection with ECT. When joining patients from the two papers into one group of 22 patients, we found that 6 had an elevated sp/s albumin ratio and that all 6 showed substantial mental confusion during the ECT series. Among the 16 patients with a normal sp/s albumin ratio only one showed mental confusion after the ECT series. During the series, about half of the patients showed confusion for a few seconds up to 15 minutes after some of the ECT sessions.

A lower [ $^{123}\text{I}$ ] $\beta$ -CIT uptake in the striatum correlated to longer disease duration. The radiotracer uptake was lower in the part of the brain contralateral to the half of the body with most PD symptoms. Patients with less advanced PD achieved the best antiparkinsonian effect of ECT. In paper V we present two patients with different favourable effects after maintenance ECT (MECT). One patient with advanced PD, who on low dose antiparkinsonian medication had disabling hypokinesia and on higher doses suffered from paranoid delusions, had a considerable antiparkinsonian effect with MECT for 18 months without mental side effects. One other patient with PD and recurrent depressions showed improvement in both conditions after a series of ECT and further improvement on successive MECT.

## DISCUSSION

Most points of discussion have already been dealt with in the separate papers and are not repeated here. The discussion is limited to a few topics.

### ***Ethical considerations on collecting copies of antiparkinsonian prescriptions.***

Copying all prescriptions on anti-parkinsonian medication six months might be regarded as an encroachment on personal integrity. The Ethical Committee of the Faculty of Health Sciences, Linköping University, The Swedish Data Inspection Board and the National Board of Health and Welfare approved the study. We regard the professional secrecy in hospitals and pharmacies as reasonably safe. Furthermore, most PD patients have symptoms that are so obvious to everyone that knowledge about a prescription does little harm.

### ***Food-Frequency Questionnaire***

For the most part, the quality of exposure measurement will determine the validity of an environmental epidemiologic study. All questionnaires and interviews rely on human knowledge and memory, and hence are subject to error. Personal or telephone interviews may also elicit underreporting of many phenomena and are susceptible to the “desirability” of the activity being reported. Self-administered questionnaires avoid interviewer influences but typically have lower response rates. The use of proxy responders often results in greater errors. We used a posted self-administered questionnaire and, when needed, written reminders. Some responders had left incompletely answered questionnaires, which we complemented with telephone interviews, sometimes with proxy responders. During the years there has been a development in methods assessing food intake. Short-term-recall and diet-record methods are generally expensive, unrepresentative of usual intake and inappropriate for assessment of past diet; thus today structured dietary questionnaires are in use. Willett (Willett 1998) refers to a study where Heady 1961 used diet records collected from British bank clerks. He demonstrated that the *frequencies* with which food was used highly correlated with the total *weights* of the same foods consumed over a several-day period, thus providing the theoretical basis for the food-frequency studies. A fundamental decision in designing a questionnaire is whether the objective is to measure the intake of a

few specific food nutrients or whether to obtain a comprehensive assessment of diet. We used a comprehensive assessment, also recommended by Willett. The interpretation of epidemiologic data on diet and disease depends directly on the validity of the methods used to measure dietary intake. This is particularly true when no association is found, as one possible explanation could be that the method used to measure diet was not able to discriminate among individuals. Validation studies of dietary questionnaires have been conducted, and different standards for comparisons have been used. As for all variables, no perfect standard exists. Validation studies published through 1989 have been summarised by Willett. Although the details of questionnaires and the populations studied have varied substantially, the correlation between nutrients assessed by food frequency questionnaires and the comparison methods, when adjusted for total energy intake, has quite consistently varied between 0.4 and 0.7. This degree of measurement error can lead to important underestimates of relative risks. Nutritional epidemiology has contributed to understanding the aetiology of many diseases. Suboptimal intake of fruit and vegetables is related to increased risk of many cancers. Thus, intake of green and yellow vegetables shows a remarkably consistent inverse association to lung cancer among men (Colditz, Stampfer, and Willett 1987). In our case-control study we have found that the control subjects consumed more meat, eggs, bread and tomatoes than the IP patients. In paper II we put forward a hypothesis of niacin as a possibly preventive factor. Further studies are desirable. The future capacity to identify those persons at genetically increased risk of disease will allow the study of gene-nutrient interactions that probably exist.

### ***High intake of tomatoes – lower risk for PD***

In 1989 Sage put forward a hypothesis that the the intake of tomatoes might explain the cause of PD (Sage 1989). The hypothesis was based on a dubious concept of PD increasing in the two previous centuries, which occurred parallel to the world-wide spread of tomatoes. To test the possible role of carotenoids in the risk of developing PD, Jiminez-Jiminez et al. compared serum levels of different carotenoids, including lycopene, in 61 PD patients using their spouses as a control group (Jiminez-Jimenez et al. 1993). Lycopene is a non-provitamin A carotenoid with antioxidant properties and is present in human blood and tissues. The major dietary sources of lycopene for the human are tomatoes. In the study Jiminez-Jimenez et al. concluded that there was no difference in the carotenoid levels between patients and controls. However, serum levels of carotenoids when patients already have the disease are not so much

of interest as the levels before they have attracted the disease. Our study instead points to tomatoes as a *protecting* agent against PD. Oxidative stress is recognised as one of the major contributors of increased *risk of cancer* and there is now an increasing number of articles suggesting oxidative stress as a *contributing factor for PD* (Ambani, Van Woert, and Murphy 1975; Cadet and Brannock 1998; Ilic et al. 1998; Jenner 1998; Mizuno, Hattori, and Matsumine 1998; Mizuno et al. 1996; Munch et al. 1998; Ziv and Melamed 1998). Several recent population studies have established a close link between dietary intake of tomatoes, a major source of the carotenoid antioxidant lycopene, and a lowered *risk of cancer* (Gerster 1997; La Vecchia 1998; La Vecchia and Tavani 1998; Rao and Agarwal 1998; Sies and Stahl 1998; Weisburger 1998). Vitamin E as an antioxidant has evoked much interest in the discussion of neuroprotection. Some authors report of a link between vitamin E deficiency and PD (Golbe, Farrell, and Davies 1990; Golbe, Farrell, and Davis 1988; Kondo 1984; Kondo 1986; Kondo and Watanabe 1993; Tangney and Tanner 1993; Tanner et al. 1988), while other cannot corroborate the association (Cerhan, Wallace, and Folsom 1994; The-Parkinson-study-group 1993; Vieregge, Mararvic, and Friedrich 1992). Three recent case-control studies (n = 57, 31 and 110, respectively) comment on dietary antioxidants and the risk for PD: 1. Scheider et al. report on daily intake of ten different antioxidants without showing any protective effect of long-term dietary antioxidant intake (Scheider et al. 1997). 2. De Rijk et al. noticed that there might be minor protective effects resulting from the intake of vitamin E but not of betacarotene but it is not indicated whether they asked about tomatoes or analysed for lycopene (de Rijk et al. 1997). 3. Logroscino et al., in a case-control study with a food-frequency questionnaire, were unable to show any significant association between PD and intake of vitamins or carotenoids but apparently did not ask about tomatoes or lycopene (Logroscino et al. 1996). However, our findings in the case-control study (Paper II), with a *significantly reduced risk of PD* when eating tomatoes daily (OR = 0.21) and each week (OR = 0.27), support the idea of tomatoes as an important source of antioxidants and tomatoes having a possible role in preventing PD.

### ***The reduced risk of smoking***

One of the most consistent findings regarding IP is the reduced risk associated with cigarette smoking. We mention some explanations for this observation that have been proposed (Pedro-Cuesta 1994; Schulte et al. 1996):

1. Recall bias; in this situation with a reduced risk there would have to be a poor recall first and foremost among the cases. Recall bias is a methodological problem common to all case-control studies.
2. Differential mortality. Smokers die earlier than non-smokers. According to Riggs no neuroprotective influence is necessary to account for the negative association between cigarette smoking and PD (Riggs 1992). The only assumption that is required is that smokers with PD experience the same premature mortality as observed in the general population.
3. Smoking may reduce the risk of developing IP by protecting the substantia nigra from the potentially toxic effects of oxidative radicals produced during the normal metabolism of dopamine. Exposures to components of cigarette smoke in MPTP-treated animals gave contradictory results, but several experiments have demonstrated protective effects of nicotine on lesioned dopaminergic neurons. (Carr and Basham 1991; Carr et al. 1992).
4. Physical or mental limitations imposed by IP result in the cessation of smoking.
5. Personality, whether or not an early manifestation of IP (personality described as "quiet", "generous", "cautious", "even tempered", "less flexible") (Hubble et al. 1993b; Jimenez-Jimenez et al. 1992; Menza et al. 1993).

To this list, we might add the possibility that an early appearance of a monoamine deficiency leads to a diminishing positive experience of smoking even before the appearance of clinical PD symptoms.

### ***Increased risk for cleaners***

To my knowledge, the observed increased risk for female cleaners (OR = 6.7; CI 95% = 1.76-30) has not been reported previously. The mean time in the occupation as a cleaner was 15.4 ± 11.6 years for the ten parkinsonian patients and 6.6 ± 2.6 years for the five controls, a fact

that points to a considerable time of occupational exposure to the cleaners. This underscores that there are reasons to further study this relationship.

### ***Some problems in rating the symptoms in PD***

We are well aware of the limitations in clinical rating scales and regard our choice as a compromise between what is theoretically desirable and practically possible.

We chose a simple clinical assessment battery with well-recognised and tested methods that were possible to utilise within 2 hours – otherwise there was a risk that the patient got too tired. One trained examiner made all ratings. Thus, we had no problems with inter-rater variability but had no measure of rater stability. Another problem with PD is that symptoms usually vary during the day and to different extents in different patients. With experience from our first study we were more aware of this problem in the second ECT study. To have at least some control over this problem the patients were asked to classify their present state as “best on”, “worst on” or “intermediate”. When possible the ratings were performed at best possible state and in the same state before and after ECT. In paper IV patients number 1, 2 and 3 were rated at the same experienced symptom level and patients 4, 5 and 6 rated themselves on a higher (“best on”) level after ECT. This points to an inherent problem as the ECT treatment increases the percentage of “normal movement hours”, and thereby diminishing the chance of measuring at the same experienced symptom level. A third problem is the patients capacity to mobilise energy and will to perform at the top of their ability. There is an obvious examiner-patient interaction effect. The more the examiner can encourage the tested person, the better they will perform. It is difficult to check for this in a scientific way but we tried to give the same amount of encouragement at every test situation and the “examiner” was the same for all patients on all occasions.

### ***Lumbar puncture***

In a series of papers Nordin and co-workers point to problems in measurements of concentrations of monoamines in CSF (Eklundh et al. 1996; Nordin 1988; Nordin 1989; Nordin 1991; Nordin 1993; Nordin and Eklundh 1996; Nordin et al. 1995; Nordin, Lindstrom, and Wieselgren 1996; Nordin, Swedin, and Zachau 1992). They point out the circumstance that many factors, for example diet, seasonal variation, atmospheric pressure, motility, gender, age, height, body weight, site of puncture, position of lumbar puncture needle and tapping

time, influence the CSF concentrations of various metabolites. The magnitude of all these influences has not been unequivocally established and, for example, others have found no, or mild, correlation between atmospheric pressure and HVA and HMPG (Faustman et al. 1993; Heilig, Månsson, and Blennow 1996). We have made our lumbar punctures and handled the CSF in a controlled, standardised way (see methods) but did not register the tapping time, the atmospheric pressure and the few cases where we chose the puncture level L3-4. When CSF analyses concern comparisons between values before and after ECT, many of the doubts stand aside since the patients are their own controls. When CSF analyses concern comparisons between groups with longer and shorter duration of positive clinical effect of ECT, some of the above-mentioned influences might obscure an interesting finding of a useful predictor.

### ***Neuropeptides***

During the past two decades, an increasing number of regulatory peptides have been discovered. A lower CSF level of NPY in patients suffering from major depression has been found. Furthermore, antidepressive drugs have been reported to influence neuropeptide concentrations in CNS (Wahlstedt and Heilig 1995). Carina Stenfors et al. found an increase in NPY concentrations in the hippocampus after six, but not single, ECS treatments in rat (Stenfors, Theodorsson, and Mathé 1989). In line with these findings we could show in paper III that NPY in CSF was significantly elevated after a series of ECT in non-depressed patients. NPY has been associated with, for example, the hypothalamic-pituitary-adrenal axis, food intake, depressive illness and anxiety. The possible role played by NPY in PD has to be further studied.

### ***Beta-CIT***

After the start of our study Müller et al. published a report on 34 previously untreated, idiopathic parkinsonian patients (Müller et al. 1998). They also found a side-to-side difference in PD patients and correlation between scores of UPDRS and [<sup>123</sup>I]β-CIT uptake. Some speculations about the influence of anti-PD medication and uptake of dopamine-transporter-binding radioligands have been addressed in two studies. The effect of bromocriptine on [<sup>123</sup>I]β-CIT uptake has not been studied as far as we know but has been studied with two other radioligands, WIN 35.428 in mouse (Scheffel et al. 1996) and

[3H]TBZOH in rat (Naudon, Leroux-Nicollet, and Costentin 1994), and no effect in binding was seen. In addition, nonspecific effects of L-dopa could interfere with [<sup>123</sup>I]β-CIT binding. In baboons Laruelle et al. were unable to produce displacement of [<sup>123</sup>I]β-CIT activity from brains in animals receiving L-dopa infusions during the plateau phase of [<sup>123</sup>I]β-CIT imaging (Laruelle et al. 1993). Four of our patients were treated with bromocriptine and/or selegiline. Both selegiline and bromocriptine affect dopaminergic systems but we could not see any influence on [<sup>123</sup>I]β-CIT in our patients. Many [<sup>123</sup>I]β-CIT SPECT studies used triple-head SPECT systems (Marek et al. 1996; Rinne et al. 1995; Seibyl et al. 1995). According to Müller et al. in the recent study mentioned above that a single-head γ-camera in combination with [<sup>123</sup>I]β-CIT could help to distinguish patients with PD from healthy subjects and to assess the intensity of PD. In contrast to studies with triple-head SPECT systems, single-head systems are not able to discriminate [<sup>123</sup>I]β-CIT uptake between the putamen and the caudate.

### ***Side effects of ECT in PD***

In paper III we report on five patients who developed *mental confusion* in connection with ECT. All five and none of the other eleven in the series showed an elevated sp/s albumin ratio. In three patients the confusion disappeared within the first day of ECT and the other two had fluctuating confusion for two weeks.

In our second study on ECT (paper IV) one patient had a history of earlier confusional episodes. He had signs of BBB damage (elevated sp/s albumin) and developed temporary confusion after ECT. One patient without indication of BBB damage showed some transient confusion after ECT. For both, their relatives reported intellectual improvement after ending the ECT series.

Andersen et al. (Andersen et al. 1987) excluded patients with signs of dementia or confusion from their study, and Douyon et al. (Douyon et al. 1989) used a “just-above-threshold dosing approach” to ECT because of PD patients’ “proclivity to develop dementia or confusion”.

The L-dopa dose ranged from 200-2000 mg/day. However, Douyon’s group noticed confusion during the course of ECT in three of seven patients. This finding was also observed in five of Andersen’s eleven patients. Seven of the eight patients in these two studies who showed confusion were treated with bilateral electrode placement. Kellner et al. (Kellner et al. 1994) point to the possibility that this delirium may be related to increased dopaminergic tone. PD patients may also be at increased risk of cognitive dysfunction during

ECT, based on the findings that patients with basal ganglia disease are more sensitive to ECT-induced cognitive effects. Figiel et al. (Figiel 1992) have reported on 20 patients with depression and PD treated with unilateral electrode placements, a “moderately suprathreshold“ stimulus. He compared them with 20 patients with earlier CVI and depression receiving the same treatment. Interictal ECT-induced delirium occurred in 5 of the CVI-patients and 17 of the PD-patients. The authors speculate that depressed patients with PD may be at greater risk of developing this complication of ECT. The L-dopa dose is not stated but in an earlier report (Figiel et al. 1991) with seven depressed PD patients receiving ECT the dose range was 300-1500 mg/day, i.e. in most patients higher doses than we used. Zervas and Fink suggest that the mechanism for the emergence of delirium might be related to the interaction of ECT and L-dopa (Zervas and Fink 1991; Zervas and Fink 1992). If doses of L-dopa are high, delirium occurs. If doses are reduced by half, delirium does not occur.

In our experience, the occurrence of delirium is much lower if the L-dopa dose is lowered to the least effective dose before the first ECT. If the patient and relatives are informed of the possibility of transitory delirium in advance, it is a well-tolerated calculated risk.

Although we have tried to have a low L-dopa dosage, we have noticed some cases with increased involuntary movements after ECT. Douyon et al (Douyon et al. 1989) found that two of their patients developed severe dyskinesias that disappeared after their levodopa doses were reduced by half. Holcomb et al. described an exacerbation of pre-existing tardive dyskinesia during the course of ECT in their report on a patient with delusional depression and PD (Holcomb, Sternberg, and Heninger 1983).

Based on the facts in this paragraph I would recommend initial unilateral ECT, reduction of dopaminergic medication to the lowest possible level before ECT and preparedness for further dose reduction in case of delirium or hyperkinesias.

### ***Why ECT in PD? Why not?***

Even in some recent reviews on general treatment of PD, ECT as a treatment for PD has not, or only casually, been noticed (Fahn 1996; Olanow and Koller 1998). Why is the spread of ECT in PD so relatively restricted? There are many answers. In many countries there is a resistance to ECT. This can be based on the early primitive methods used with accompanying risks of fractures, impaired memory function, delirium etc. Fractures have disappeared after

introduction of anaesthesia and muscle relaxation. With modern treatment techniques memory function is back to baseline after 1-2 weeks (d'Elia 1994). Furthermore, doctors and patients may find it complicated to involve expertise on general anaesthesia and ECT treatment. The cost for 2 weeks as an in-patient and the cost for the treatment might evoke hesitation. Some movies such as "One flew over the cuckoo's nest" (Forman 1975) have presented a horror-filled and misleading picture of modern ECT treatment. ECT in depression has been investigated in many publications, and the treatment is regarded as very safe, with fatal incidence of zero in Sweden and three per 100,000 treatments in USA (d'Elia and Ottosson 1982).

Another serious drawback is the individually unpredictable duration of effect. Two of our patients with the most striking improvements had very short effect duration. One of the patients was able to leave her wheelchair and felt bitterness when the effect faded away quickly. ECT has an initial positive effect in almost all cases. The duration of the treatment effect in our studies is 3-18 months in 55% of the patients.

There are considerable data supporting a true antiparkinsonian effect of ECT. Definite favourable prognostic features are still lacking although advanced age, on-off phenomena, and less pronounced disease speak in favour of a positive outcome. In my opinion the treatment alternatives for PD patients at the advanced "stages of complication" are few, expensive and accompanied with modest effect. ECT is an easily available, safe and comparatively cheap method. The ECT treatment in PD deserves wider recognition than at present. I recommend it as an alternative in cases where modern medication is insufficient and/or associated with intolerable side effects.

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## REFERENCES

- Aarsland, Dag, Jan Petter Larsen, and Elise Tandberg. 1993. Electroconvulsive treatment in parkinsonism. *Tidsskr Nor Laegeforen* 113: 3564-6.
- Aarsland, D, J P Larsen, Ö Waage, and J Langeveld. 1997. Maintenance Electroconvulsive Therapy for Parkinson's disease. *Convulsive Therapy* 13: 274-277.
- Abrams, R. 1989. ECT for Parkinson's disease [editorial]. *Am J Psychiatry* 146, no. 11: 1391-3.
- Ahmadi, Ahmad, Mats Fredrikson, Helena Jerregård, Anita Åkerbäck, Per-Arne Fall, Agneta Rannung, Olav Axelson, and Peter Söderkvist. 1999. Microsomal epoxide hydrolase and glutathione S-transferase M1 polymorphisms; Susceptibility to Parkinson's disease and age of onset. *Manuscript*.
- Ambani, L. M., M. H. Van Woert, and S. Murphy. 1975. Brain peroxidase and catalase in Parkinson disease. *Arch Neurol* 32, no. 2: 114-8.
- Ananth, J., D. Samra, and T. Kolivakis. 1979. Amelioration of drug-induced parkinsonism by ECT. *Am J Psychiatry* 136, no. 8: 1094.
- Andersen, K, J Balldin, CG Gottfries, A-K Granérus, K Modigh, L Svennerholm, and A Wallin. 1987. A double-blind evaluation of electroconvulsive therapy in Parkinson's disease with "on-off" phenomena. *Acta Neurol Scand* 76: 191-199.
- Aquilonius, S-M and P Hartvig. 1986. A Swedish county with unexpectedly high utilization of anti-Parkinsonian drugs. *Acta Neurol Scand* 74: 379-382.
- Arbman, Gunnar, Olav Axelson, Mats Fredriksson, Erik Nilsson, and Rune Sjö Dahl. 1993. Do occupational factors influence the risk of colon cancer in different ways? *Cancer* 72, no. 9: 2543-2549.
- Ashok, P. P., K. Radhakrishnan, R. Sridharan, and M. E. Mousa. 1986. Epidemiology of Parkinson's disease in Benghazi, North-East Libya. *Clin Neurol Neurosurg* 88, no. 2: 109-13.
- Asnis, G. 1977. Parkinson's disease, depression, and ECT: a review and case study. *Am J Psychiatry* 134, no. 2: 191-5.
- Atre-Vaidya, N. and V. C. Jampala. 1988. Electroconvulsive therapy in parkinsonism with affective disorder. *Br J Psychiatry* 152: 55-8.
- Balldin, J, S Edén, A Granérus, K Modigh, A Svanborg, J Wålinder, and L Wallin. 1980. Electroconvulsive therapy in Parkinson's syndrome with "on-off" phenomenon. *J Neural Transm* 47: 11-21.

- Balldin, J., A.K. Granérus, G. Lindstedt, K. Modigh, and J. Wålinder. 1982. Neuroendocrine evidence for increased responsiveness of dopamine receptors in humans following electroconvulsive therapy. *Psychopharmacology* 76: 371-376.
- Balldin, J., A.-K. Granérus, G. Lindstedt, K. Modigh, and J. Wålinder. 1981. Predictors for improvement after electroconvulsive therapy in Parkinsonian patients with on-off symptoms. *J Neural Transm* 52: 199-211.
- Barbeau, A., M. Roy, G. Bernier, G. Campanella, and S. Paris. 1987. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can J Neurol Sci* 14, no. 1: 36-41.
- Barcia, D. and F. Martinez Pardo. 1978. [Depressive pictures in Parkinson's disease treated with electroshock]. *Arch Neurobiol (Madr)* 41, no. 5: 393-8.
- Barkai, AI, M Durkin, and H D Nelson. 1990. Localized alterations of dopamine receptor binding in rat brain by repeated electroconvulsive shock: an autoradiographic study. *Brain Research* 529: 208-13.
- Baruch, P., R. Jouvent, R. Vindreau, C. Drouillon, D. Widlöcher, and Y. Agid. 1985. Improvement of parkinsonism in ECT-treated depressed patients: Parkinson's disease or depression-related extrapyramidal disorder? In *IVth World Congress of Biological Psychiatry*, ed. C. Shagass:426. New York: Elsevier.
- Benabid, A. L., A. Benazzouz, D. Hoffman, P. Limousin, P. Krack, and P. Pollak. 1998. Long-term electrical inhibition of deep brain targets in movement disorders. *Mov Disord* 13, no. Suppl 3: 119-125.
- Berger, M. and D. A. de Soto. 1990. The use of ECT for Parkinson symptoms in a nondepressed patient [letter]. *Psychosomatics* 31, no. 4: 465-6.
- Bharucha, N.E., E.P. Bharucha, A.E. Bharucha, A.V. Bhise, and B.S. Schoenberg. 1988. Prevalence of Parkinson's disease in the Parsi Community of Bombay, India. *Arch Neurol* 45: 1321-1323.
- Birkett, D.P. 1991. Electroconvulsive therapy and Parkinson's disease. *Clinical Gerontologist* 10, no. 4: 11-21.
- Bolwig, T. G., M. M. Hertz, and J. Holm-Jensen. 1977. Blood-brain barrier during electroshock seizures in the rat. *Eur J Clin Invest* 7, no. 2: 95-100.
- Brooks, D. J. 1991. Detection of preclinical Parkinson's disease with PET. *Neurology* 41, no. 5 Suppl 2: 24-7.
- Brown, G.L. 1975. Parkinsonism, depression and ECT (letter to the editor). *Am J Psychiatry* 132, no. 10: 1084.

- Burke, W.J. , J . Peterson, and E.H . Rubin. 1988. Electroconvulsive therapy in the treatment of combined depression and Parkinson's disease. *Psychosomatics* 29: 341-346.
- Cadet, J. L. and C. Brannock. 1998. Free radicals and the pathobiology of brain dopamine systems. *Neurochem Int* 32, no. 2: 117-31.
- Carr, L. A. and J. K. Basham. 1991. Effects of tobacco smoke constituents on MPTP-induced toxicity and monoamine oxidase activity in the mouse brain. *Life Sci* 48, no. 12: 1173-7.
- Carr, L. A., J. K. Basham, B. K. York, and P. P. Rowell. 1992. Inhibition of uptake of 1-methyl-4-phenylpyridinium ion and dopamine in striatal synaptosomes by tobacco smoke components. *Eur J Pharmacol* 215, no. 2-3: 285-7.
- Cerhan, J R, R B Wallace, and A R Folsom. 1994. Antioxidant intake and risk of Parkinson's disease (PD) in older women [abstract]. *Am J Epidemiol* 139: 65.
- Colditz, G. A., M. J. Stampfer, and W. C. Willett. 1987. Diet and lung cancer. A review of the epidemiologic evidence in humans. *Arch Intern Med* 147, no. 1: 157-60.
- Cummings, J. L. 1992. Depression and Parkinson's disease: a review. *Am J Psychiatry* 149, no. 4: 443-54.
- Dam, H., H. Pakkenberg, and T. G. Bolwig. 1992. [Electric stimulation (ECT) in Parkinson disease]. *Ugeskr Laeger* 154, no. 4: 183-7.
- de Rijk, M. C., M. M. Breteler, J. H. den Breeijen, L. J. Launer, D. E. Grobbee, F. G. van der Meche, and A. Hofman. 1997. Dietary antioxidants and Parkinson disease. The Rotterdam Study. *Arch Neurol* 54, no. 6: 762-5.
- d'Elia, Giacomo. 1994. *ECT- en behandlingsmetod i den psykiatriska vården*. Socialstyrelsen följer upp och utvärderar. Stockholm: Socialstyrelsen: 1994:5.
- d'Elia, G. and J. O. Ottosson. 1982. [Electroconvulsive therapy - a review]. *Lakartidningen* 79, no. 19: 1903-5.
- Doll, R. 1976. Comparison between registries age-standardized rates. In *Cancer incidence in five continents*, ed. John Waterhouse, Calum Muir, Pelayo Correa, and Jean Powell, III:453-459. Lyon: International agency for research on cancer.
- Douyon, R., M. Serby, B. Klutchko, and J. Rotrosen. 1989. ECT and Parkinson's disease revisited: a "naturalistic" study. *Am J Psychiatry* 146, no. 11: 1451-5.
- Dysken, M., H. M. Evans, C. H. Chan, and J. M. Davis. 1976. Improvement of depression and parkinsonism during ECT: a case study. *Neuropsychobiology* 2, no. 2-3: 81-6.
- Eklundh, T., M. Eriksson, S. Sjöberg, and C. Nordin. 1996. Monoamine precursors, transmitters and metabolites in cerebrospinal fluid: a prospective study in healthy male subjects. *J Psychiatr Res* 30, no. 3: 201-8.

- Emery, Peter W. 1996. ECT for Parkinson's disease. Reconsidering an old concept. *Brattleboro Retreat Psychiatry Review* 5, no. 2: 1-6.
- Eriksson, T., T. Magnusson, A. Carlsson, A. Linde, and A. K. Granerus. 1984. "On-off" phenomenon in Parkinson's disease: correlation to the concentration of dopa in plasma. *J Neural Transm* 59, no. 3: 229-40.
- Faber, R. and M. R. Trimble. 1991. Electroconvulsive therapy in Parkinson's disease and other movement disorders. *Mov Disord* 6, no. 4: 293-303.
- Fahn, S. 1992. Adverse effects of levodopa. In *The scientific basis for the treatment of Parkinson's disease.*, ed. C.W. Olanow and A.N. Lieberman:89-112. Carnforth, England: Parthenon.
- Fahn, S. 1996. Controversies in the therapy of Parkinson's disease. *Adv Neurol* 69: 477-86.
- Fahn, Stanley, Richard L Elton, and Members of the UPDRS Development Committee. 1987. Unified Parkinson's disease rating scale. In *Recent developments in Parkinson's disease*, ed. S Fahn, CD Marsden, DB Calne, and A Lieberman, II:153-163. Florham Park, New Jersey: Macmillan Health Care Information.
- Fall, P.- A., O. Axelson, M. Fredriksson, G. Hansson, B. Lindvall, J. E. Olsson, and A.-K. Granerus. 1996. Age-standardized incidence and prevalence of Parkinson's disease in a Swedish Community. *J Clin Epidemiol* 49, no. 6: 637-41.
- Fall, P.-A., R. Ekman, A.-K. Granerus, L.-H. Thorell, and J. Wålinder. 1995. ECT in Parkinson's disease. Changes in motor symptoms, monoamine metabolites and neuropeptides. *J Neural Transm Park Dis Dement Sect* 10, no. 2-3: 129-40.
- Fall, P.-A., M. Fredrikson, O. Axelson, and A.-K. Granérus. 1999. Nutritional and occupational factors influencing the risk of Parkinson's disease: A case-control study in southeastern Sweden. *Movement Disorders* 14, no. 1: 28-37.
- Fall, Per-Arne and Ann-Kathrine Granérus. 1999b. Maintenance ECT in Parkinson's disease. *Manuscript* .
- Fall, Per-Arne, Ann-Kathrine Granérus, Göran Granérus, and Stefan Ekberg. 1999a. ECT in Parkinson's disease - dopamine transporter visualised by 123I-beta-CIT SPECT - a pilot study. *Manuscript* .
- Faustman, W.O., P.J. Elliot, D.L. Ringo, and K.F. Faull. 1993. CSF 5HIAA and atmospheric pressure: Failure to replicate. *Biol Psychiatry* 33: 61-62.
- Fearnley, Julian and Andrew J. Lees. 1997. Parkinson's disease: Neuropathology. In *Movement Disorders: Neurologic Principles and Practice*, ed. Ray L Watts and William C. Koller:263-278. New York: McGraw-Hill.

- Figiel, G. S. 1992. ECT and delirium in Parkinson's disease [letter]. *Am J Psychiatry* 149, no. 12: 1759.
- Figiel, G. S., M. A. Hassen, C. Zorumski, K. R. Krishnan, P. M. Doraiswamy, M. R. Jarvis, and D. S. Smith. 1991. ECT-induced delirium in depressed patients with Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 3, no. 4: 405-11.
- Folstein, MF, SE Folstein, and PR McHugh. 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189-198.
- Forman, Milos. 1975. One flew over the cuckoos nest (Movie).
- Forno, L. S. 1987. The Lewy body in Parkinson's disease. *Adv Neurol* 45: 35-43.
- Fromm, G.H. 1959. Observations of the effect of electroshock treatment on patients with parkinsonism. *Bull Tulane Univ Med Faculty* 18: 71-73.
- Gallinek, A. 1947. Electric convulsive therapy in geriatrics. *NY State J Med* 47: 1233-1241.
- Gasser, T. 1998. Genetics of Parkinson's disease. *Clin Genet* 54, no. 4: 259-65.
- Gerster, H. 1997. The potential role of lycopene for human health. *J Am Coll Nutr* 16, no. 2: 109-26.
- Golbe, Lawrence I, Thimothy M Farrell, and Patricia H Davies. 1990. Follow-up study of early-life protective and risk factors in Parkinson's disease. *Movement Disorders* 5, no. 1: 66-70.
- Golbe, Lawrence I, Timothy M Farrell, and Patricia H Davis. 1988. Case-control study of early life factors in Parkinson's disease. *Arch Neurol* 45: 1350-1353.
- Goswami, U., S. Dutta, K. Kuruvilla, E. Papp, and A. Perenyi. 1989. Electroconvulsive therapy in neuroleptic-induced parkinsonism. *Biol Psychiatry* 26, no. 3: 234-8.
- Gottfries, C.-G., G Bråne, B Gullberg, and G Steen. 1982. A new rating scale for dementia syndromes. *Arch Gerontol Geriatr* 1: 311-330.
- Granérus, A. K. 1978. Factors influencing the occurrence of "on-off" symptoms during long-term treatment with L-dopa. *Acta Med Scand* 203, no. 1-2: 75-85.
- Gudmunsson, K.R. 1967. A clinical survey of Parkinsonism in Iceland. *Acta Neurol Scand* 33: 9-61.
- Harada, H., S. Nishikawa, and K. Takahashi. 1983. Epidemiology of Parkinson's disease in a Japanese city. *Arch Neurol* 40, no. 3: 151-4.
- Heilig, M., J.E. Månsson, and K. Blennow. 1996. Cerebrospinal fluid monoamine metabolites and atmospheric pressure. *Biol Psychiatry* 39: 299-301.

- Hermesh, H., D. Aizenberg, G. Friedberg, M. Lapidot, and H. Munitz. 1992. Electroconvulsive therapy for persistent neuroleptic-induced akathisia and parkinsonism: a case report. *Biol Psychiatry* 31, no. 4: 407-11.
- Hertzman, Clyde, Michele Wiens, David Bowering, Barry Snow, and Donald Calne. 1990. Parkinson's disease: A case-control study of occupational and environmental risk factors. *Am J Ind Med* 17(3): 349-355.
- Hertzman, Clyde, Michele Wiens, Barry Snow, Shona Kelly, and Donald Calne. 1994. A case-control study of Parkinson's disease in a horticultural region of British Columbia. *Mov Disord* 9, no. 1: 69-75.
- Ho, Suzanne C., Jean Woo, and Chi M. Lee. 1989. Epidemiologic study of Parkinson's disease in Hong Kong. *Neurology* 39: 1314-1318.
- Hoehn, M.M. and M.D. Yahr. 1967. Parkinsonism : onset, progression and mortality. *Neurology* 17: 427-442.
- Holcomb, Henry H., David E. Sternberg, and George R. Heninger. 1983. Effects of electroconvulsive therapy on mood, parkinsonism and tardive dyskinesia in a depressed patient: ECT and dopamine systems. *Biological Psychiatry* 19, no. 8: 865-873.
- Hubble, JP, T Cao, RES Hassanein, JS Neuberger, and WC Koller. 1993a. Risk factors for Parkinson's disease. *Neurology* 43: 1693-1697.
- Hubble, J.P., R. Venkatesh, R.E. Hassanein, C. Gray, and W.C. Koller. 1993b. Personality and depression in Parkinson's disease. *Journal of Nervous & Mental Disease* 181, no. 11: 657-662.
- Hughes, A. J., S. E. Daniel, L. Kilford, and A. J. Lees. 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases [see comments]. *J Neurol Neurosurg Psychiatry* 55, no. 3: 181-4.
- Hurwitz, T. A., D. B. Calne, and K. Waterman. 1988. Treatment of dopaminomimetic psychosis in Parkinson's disease with electroconvulsive therapy. *Can J Neurol Sci* 15, no. 1: 32-4.
- Ilic, T., M. Jovanovic, A. Jovicic, and M. Tomovic. 1998. Oxidative stress and Parkinson's disease. *Vojnosanit Pregl* 55, no. 5: 463-8.
- Irvin, S. M. 1997. Treatment of depression with outpatient electroconvulsive therapy. *Aorn J* 65, no. 3: 573-8, 581-2.
- Jaeckle, R. S. and S. C. Dilsaver. 1986. Covariation of depressive symptoms, parkinsonism, and post-dexamethasone plasma cortisol levels in a bipolar patient: simultaneous response to ECT and lithium carbonate. *Acta Psychiatr Scand* 74, no. 1: 68-72.

- Jenner, P. 1998. Oxidative mechanisms in nigral cell death in Parkinson's disease. *Mov Disord* 13 Suppl 1: 24-34.
- Jimenez-Jimenez, F. J., J. A. Molina, P. Fernandez-Calle, A. Vazquez, F. Cabrera-Valdivia, M. J. Catalan, E. Garcia-Albea, F. Bermejo, and R. Codoceo. 1993. Serum levels of beta-carotene and other carotenoids in Parkinson's disease. *Neurosci Lett* 157, no. 1: 103-6.
- Jimenez-Jimenez, F. J., J. Santos, F. Zancada, J. A. Molina, J. Irastorza, A. Fernandez-Ballesteros, and A. Roldan. 1992. "Premorbid" personality of patients with Parkinson's disease. *Acta Neurol (Napoli)* 14, no. 3: 208-14.
- Kalinowsky, L.B. 1949. Die Electrokrampfbehandlung in ihrer Beziehung zur Neurologie. *Monatsschr Psychiatr Neurol* 177: 268-279.
- Kapur, S. and J. J. Mann. 1992. Role of the dopaminergic system in depression. *Biol Psychiatry* 32, no. 1: 1-17.
- Kapur, S. and J.J. Mann. 1993. Antidepressant action and the neurobiologic effects of ECT: Human studies. In *The clinical science of electroconvulsive therapy*, ed. C E Coffey:235-250. Washington: American Psychiatric Press, Inc.
- Kellner, C. H., M. D. Beale, J. T. Pritchett, H. J. Bernstein, and C. M. Burns. 1994. Electroconvulsive therapy and Parkinson's disease: the case for further study. *Psychopharmacol Bull* 30, no. 3: 495-500.
- Kessler, I.I. 1972. Epidemiologic studies of Parkinson's disease. 3. A community-based survey. *Am J Epidemiol* 96, no. 4: 242-54.
- Koller, W., B. Vetere-Overfield, and C. Gray. 1990. Environmental risk factors in Parkinson's disease. *Neurology* 40: 1218-1221.
- Koller, W. C., J. W. Langston, J. P. Hubble, I. Irwin, M. Zack, L. Golbe, L. Forno, J. Ellenberg, L. Kurland, A. J. Rutenber, and et al. 1991. Does a long preclinical period occur in Parkinson's disease? *Neurology* 41, no. 5 Suppl 2: 8-13.
- Kondo, K. 1984. Epidemiological clues for the etiology of Parkinson's disease. *Adv Neurol* 40: 345-351.
- Kondo, Kiyotaro. 1986. Epidemiological evaluation of risk factors in Parkinson's disease. In *Parkinsons' disease*, ed. MD Yahr and KJ Bergman, 45:289-293. New York: Raven Press.
- Kondo, K and K Watanabe. 1993. Lifestyles, risk factors, and inherited predispositions in Parkinson's disease. Preliminary report of a case-control study. *Adv Neurol* 60: 346-351.
- Kurland, L.T. 1958. Epidemiology: Incidence, geographic distribution and genetic considerations. In *Pathogenesis and treatment of parkinsonism*, ed. WS Fields:5-49. Springfield Ill: Charles C Thomas.

- Kurtzke, J. F. and F. M. Murphy. 1990. The changing patterns of death rates in parkinsonism. *Neurology* 40, no. 1: 42-9.
- La Vecchia, C. 1998. Mediterranean epidemiological evidence on tomatoes and the prevention of digestive-tract cancers. *Proc Soc Exp Biol Med* 218, no. 2: 125-8.
- La Vecchia, C. and A. Tavani. 1998. Fruit and vegetables, and human cancer. *Eur J Cancer Prev* 7, no. 1: 3-8.
- Laitinen, L. V., A. T. Bergenheim, and M. I. Hariz. 1992. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 76, no. 1: 53-61.
- Langston, W. J., P. Ballard, and J.W. Tetrud. 1983. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219: 979-980.
- Laruelle, M., R. M. Baldwin, R. T. Malison, Y. Zea-Ponce, S. S. Zoghbi, M. S. al-Tikriti, E. H. Sybiriska, R. C. Zimmermann, G. Wisniewski, J. L. Neumeyer, and et al. 1993. SPECT imaging of dopamine and serotonin transporters with [<sup>123</sup>I]beta- CIT: pharmacological characterization of brain uptake in nonhuman primates. *Synapse* 13, no. 4: 295-309.
- Lebebsohn, Z.M. and R.B. Jenkins. 1975. Improvement of parkinsonism in depressed patients treated with ECT. *Am J Psychiatry* 132: 283-285.
- Lees, A. J. 1995. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. Parkinson's Disease Research Group of the United Kingdom. *Bmj* 311, no. 7020: 1602-7.
- Levy, L. A., J. M. Savit, and M. Hodes. 1983. Parkinsonism: improvement by electroconvulsive therapy. *Arch Phys Med Rehabil* 64, no. 9: 432-3.
- Li, J. W., Bruce Schoenberg, C. Wang, X. Cheng, D. Rui, C. Bolis, and Devera Schoenberg. 1985. A prevalence survey of Parkinson's disease and other movement disorders in the People's Republic of China. *Arch Neurol* 42, no. July: 655-657.
- Lilienfeld, D. E., E. Chan, J. Ehland, J. Godbold, P. J. Landrigan, G. Marsh, and D. P. Perl. 1990. Two decades of increasing mortality from Parkinson's disease among the US elderly. *Arch Neurol* 47, no. 7: 731-4.
- Lindvall, O. and A. Bjorklund. 1989. Transplantation strategies in the treatment of Parkinson's disease: experimental basis and clinical trials. *Acta Neurol Scand Suppl* 126: 197-210.
- Lindvall, O., S. Rehncrona, P. Brundin, B. Gustavii, B. Astedt, H. Widner, T. Lindholm, A. Bjorklund, K. L. Leenders, J. C. Rothwell, and et al. 1989. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. *Arch Neurol* 46, no. 6: 615-31.

- Link, H. and G. Tibbling. 1977. Principles of albumin and IgG analyses in neurological disorders. II. Relations of the concentrations of the proteins in serum and cerebrospinal fluid. *Scand J Clin Lab Invest* 37: 391-397.
- Lipper, S. and P. C. Bermanzohn. 1975. Letter: Electroconvulsive therapy in patients with parkinsonism. *Am J Psychiatry* 132, no. 4: 457.
- Logroscino, Giancarlo, Karen Marder, Lucien Cote, Ming-Xin Tang, Steve Shea, and Richard Mayeux. 1996. Dietary lipids and antioxidants in Parkinson's disease: A population-based, case-control study. *Ann Neurol* 39: 89-94.
- Major, L. F. 1984. Electroconvulsive therapy in the 1980s. *Psychiatr Clin North Am* 7, no. 3: 611-23.
- Marek, K. L., J. P. Seibyl, S. S. Zoghbi, Y. Zea-Ponce, R. M. Baldwin, B. Fussell, D. S. Charney, C. van Dyck, P. B. Hoffer, and R. P. Innis. 1996. [<sup>123</sup>I] beta-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. *Neurology* 46, no. 1: 231-7.
- Marsden, C. D. 1994. Parkinson's disease. *J Neurol Neurosurg Psychiatry* 57, no. 6: 672-81.
- Marttila, R. 1992. Epidemiology. In *Handbook of Parkinson's Disease*, ed. W.C. Koller:35-57. New York: Marcel Dekker.
- Marttila, R.J. and U.K. Rinne. 1976. Epidemiology of Parkinson's disease in Finland. *Acta Neurol Scand* 53: 81-102.
- Mayeux, R., J. Denaro, N. Hemenegildo, K. Marder, M. X. Tang, L. J. Cote, and Y. Stern. 1992. A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. *Arch Neurol* 49, no. 5: 492-7.
- Melcon, M. O., D. W. Anderson, R. H. Vergara, and W. A. Rocca. 1997. Prevalence of Parkinson's disease in Junin, Buenos Aires Province, Argentina. *Mov Disord* 12, no. 2: 197-205.
- Menza, M. A., L. I. Golbe, R. A. Cody, and N. E. Forman. 1993. Dopamine-related personality traits in Parkinson's disease. *Neurology* 43, no. 3 Pt 1: 505-8.
- Mizuno, Y., N. Hattori, and H. Matsumine. 1998. Neurochemical and neurogenetic correlates of Parkinson's disease. *J Neurochem* 71, no. 3: 893-902.
- Mizuno, Yoshikuni, Shin-Ichirou Ikebe, Nobutaka Hattori, Hideki Mochizuki, Yuko Nakagawa-Hattori, and Tomoyoshi Kond. 1996. Etiology of Parkinson's disease. In *Movement Disorders Neurologic principles and practise*, ed. Ray L. Watts and William C. Koller:161-182. New York: McGraw-Hill.

- Modigh, K. 1975. Electroconvulsive shock and postsynaptic catecholamine effects: Increased psychomotor stimulant action of apomorphine and clonidine in reserpine pretreated mice by repeated ECS. *J. Neural Transm.* 36: 19-32.
- Moellentine, C., T. Rummans, J. E. Ahlskog, W. S. Harmsen, V. J. Suman, M. K. O'Connor, J. L. Black, and T. Pileggi. 1998. Effectiveness of ECT in patients with parkinsonism. *J Neuropsychiatry Clin Neurosci* 10, no. 2: 187-93.
- Montgomery, S.A. and M. Åsberg. 1979. A new depression scale designed to be sensitive to change. *Br J. Psychiatry* 134: 382-389.
- Morgante, L., W. A. Rocca, A. E. Di Rosa, P. De Domenico, F. Grigoletto, F. Meneghini, A. Reggio, G. Savettieri, M. G. Castiglione, F. Patti, and et al. 1992. Prevalence of Parkinson's disease and other types of parkinsonism: a door-to-door survey in three Sicilian municipalities. The Sicilian Neuro-Epidemiologic Study (SNES) Group. *Neurology* 42, no. 10: 1901-7.
- Morrish, P. K., G. V. Sawle, and D. J. Brooks. 1995. Clinical and [18F] dopa PET findings in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* 59, no. 6: 597-600.
- Morrish, P. K., G. V. Sawle, and D. J. Brooks. 1996. An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain* 119, no. Pt 2: 585-91.
- Munch, G., M. Gerlach, J. Sian, A. Wong, and P. Riederer. 1998. Advanced glycation end products in neurodegeneration: more than early markers of oxidative stress? *Ann Neurol* 44, no. 3 Suppl 1: S85-8.
- Mutch, W. J., I. Dingwall-Fordyce, A. W. Downie, J. G. Paterson, and S. K. Roy. 1986. Parkinson's disease in a Scottish city. *Br Med J (Clin Res Ed)* 292, no. 6519: 534-6.
- Müller, T. , J. Farahati, W. Kuhn, E. G. Eising, H. Przuntek, C. Reiners, and H. H. Coenen. 1998. [123I]beta-CIT SPECT visualizes dopamine transporter loss in de novo. *Eur Neurol* 39, no. 1: 44-8.
- Naudon, L., I. Leroux-Nicollet, and J. Costentin. 1994. Short-term treatments with haloperidol or bromocriptine do not alter the density of the monoamine vesicular transporter in the substantia nigra. *Neurosci Lett* 173, no. 1-2: 1-4.
- Nilsson, D., L.E. Hansson, K. Johansson, C. Nystrom, L. Paalzow, and S.M. Aquilonius. 1998. Long-term intraduodenal infusion of a water based levodopa-carbidopa dispersion in very advanced Parkinson's disease. *Acta Neurol Scand* 97, no. 3: 175-183.
- Nomikos, G.G., A.P. Zis, G. Damsma, and H.C. Fibiger. 1991. Electroconvulsive shock produces large increases in interstitial concentrations of dopamine in rat striatum: an in vivo microdialysis study. *Neuropsychopharmacology* , no. 4: 65-69.

- Nordin, C. 1988. Relationships between clinical symptoms and monoamine metabolite concentrations in biochemically defined subgroups of depressed patients. *Acta Psychiatr Scand* 78, no. 6: 720-9.
- Nordin, C. 1989. Gradients of monoamine metabolites in relation to position of the lumbar puncture needle. *Biol Psychiatry* 25, no. 4: 513-6.
- Nordin, C. 1991. CSF spinal gradients of 5-HIAA [letter]. *Biol Psychiatry* 29, no. 3: 302-3.
- Nordin, C. 1993. CSF/plasma ratio of 10-hydroxynortriptyline is influenced by sex and body height. *Psychopharmacology (Berl)* 113, no. 2: 222-4.
- Nordin, C. and T. Eklundh. 1996. Cerebrospinal fluid transmitter metabolites and atmospheric pressure [letter; comment]. *Biol Psychiatry* 40, no. 7: 682-4.
- Nordin, C., T. Eklundh, V. Fernstrom, A. Swedin, and A. C. Zachau. 1995. Gradients of CSF monoamine metabolites: a comparison between male and female volunteers. *J Psychiatr Res* 29, no. 2: 133-40.
- Nordin, C., L. Lindstrom, and I. M. Wieselgren. 1996. Acid monoamine metabolites in the CSF of healthy controls punctured without preceding strict bedrest: a retrospective study. *J Psychiatr Res* 30, no. 2: 127-33.
- Nordin, C., A. Swedin, and A. Zachau. 1992. CSF 5-HIAA and atmospheric pressure [letter]. *Biol Psychiatry* 31, no. 6: 644-5.
- Oh, J. J., T. A. Rummans, M. K. O'Connor, and J. E. Ahlskog. 1992. Cognitive impairment after ECT in patients with Parkinson's disease. *Am J Psychiatry* 149, no. 2: 271.
- Okada, K., S. Kobayashi, and T. Tsunematsu. 1990. Prevalence of Parkinson's disease in Izumo City, Japan. *Gerontology* 36, no. 5-6: 340-4.
- Olanow, C. Warren, Thomas B. Freeman, and Jeffrey H. Kordower. 1996. Transplantation strategies for Parkinson's disease. In *Movement Disorders Neurologic Principles and Practice*, ed. Ray L. Watts and William C. Koller:221-236. New York: McGraw-Hill.
- Olanow, C. Warren and William C. Koller. 1998. An algorithm (decision tree) for the management of Parkinson's disease: Treatment guidelines. *Neurology* 50, no. (Suppl 3): 1-57.
- Parkinson, J. 1817. *An Essay on the Shaking Palsy*. London, England: Sherwood, Neely, and Jones.
- Pedro-Cuesta, J. 1994. Risk factors of Parkinson's disease. In *Epidemiology*, ed. K. Vuylstreek and M. Hallen, 4:182-211. Amsterdam: IOS Press.
- Pridmore, S., A. Lowrie, G. Holmes, and C. Pollard. 1996. ECT in Parkinson's disease: neuropsychological response [letter]. *Convuls Ther* 12, no. 4: 257-9.

- Pridmore, Saxby, Poh Teck Yeo, and Mohamed Iqbal Pasha. 1995. Electroconvulsive Therapy for the physical signs of Parkinson's disease without depressive disorder. *J Neurol Neurosurg Psychiatry* 58: 641-2.
- Rainey, J. M., Jr. and et al. 1975. Letter: Parkinsonism masked by ECT and psychotropic medication. *Am J Psychiatry*. 132, no. 10: 1084-1085.
- Rajput, A.H., Kenneth Offord, Mary Beard, and Leonard Kurland. 1984. Epidemiology of Parkinsonism: Incidence, Classification, and Mortality. *Ann Neurol* 16: 278-282.
- Rajput, A.H., Ryan Uitti, W Stern, and W Laverty. 1986. Early onset Parkinson's disease in Saskatchewan - Environmental considerations for etiology. *Can. J. Neurol. Sci.* , no. 13: 312-316.
- Rao, A. V. and S. Agarwal. 1998. Bioavailability and in vivo antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer. *Nutr Cancer* 31, no. 3: 199-203.
- Rasmussen, K. and R. Abrams. 1991. Treatment of Parkinson's disease with electroconvulsive therapy. *Psychiatr Clin North Am* 14, no. 4: 925-33.
- Riggs, Jack E. 1992. Cigarette smoking and Parkinson's disease: The illusion of neuroprotective effect. *Clin Neuropharmacol* 15, no. 2: 88-99.
- Rinne, Juha O. , Jyrki T. Kuikka, Kim A. Bergström, and Urpo K. Rinne. 1995. Striatal dopamine disorder in different disability stages of Parkinson's disease studied with 123 I-beta-CIT SPECT. *Parkinsonism and Related Disorders Disord* 1, no. 1: 47-51.
- Rocca, Walter A., Dallas W. Anderson, Francesca Meneghini, Francesco Grigoletto, Letterio Morgante, Arturo Reggio, Giovanni Savattieri, and Raol Di Perri. 1996. Occupation, education and Parkinson's disease: A case-control study in an Italian population. *Movement Disorders* 11, no. 2: 201-206.
- Rosati, G., E. Granieri, L. Pinna, I. Aiello, R. Tola, P. De Bastiani, A. Pirisi, and M. C. Devoto. 1980. The risk of Parkinson's disease in Mediterranean people. *Neurology* 30, no. 3: 250-5.
- Sage, J. I. 1989. Tomatoes and Parkinson's disease. *Med Hypotheses* 28, no. 2: 75-9.
- Sawle, G. V. 1993. The detection of preclinical Parkinson's disease: what is the role of positron emission tomography? *Mov Disord* 8, no. 3: 271-7.
- Scheffel, U., C. Steinert, S. E. Kim, M. D. Ehlers, J. W. Boja, and M. J. Kuhar. 1996. Effect of dopaminergic drugs on the in vivo binding of [3H]WIN 35,428. *Synapse* 23, no. 2: 61-9.

Scheider, W. L., L. A. Hershey, J. E. Vena, T. Holmlund, J. R. Marshall, and Freudenheim. 1997. Dietary antioxidants and other dietary factors in the etiology of Parkinson's disease. *Mov Disord* 12, no. 2: 190-6.

Schmidt-Kastner, R., A. Tomac, B. Hoffer, S. Bektesh, B. Rosenweig, and O. Olson. 1994. Glial cell-line derived neurotrophic factor (GDNF) mRNA upregulation in striatum and cortical areas after pilocarpine-induced status epilepticus in rats. *Mol Brain Res* , no. 26: 325-330.

Schoenberg, B.S. , D.W. Anderson, and A.F. Haerer. 1985. Prevalence of Parkinson's disease in the biracial population of Copiah County, Mississippi. *Neurology* 35: 841-845.

Schulte, P.A., C.A. Burnett, M.F. Boeniger, and J. Johnson. 1996. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. *American Journal of Public Health*. 86, no. 9: 1281-1288.

Seibyl, J. P., K. L. Marek, D. Quinlan, K. Sheff, S. Zoghbi, Y. Zea-Ponce, R. M. Baldwin, B. Fussell, E. O. Smith, D. S. Charney, and et al. 1995. Decreased single-photon emission computed tomographic [123I]beta-CIT striatal uptake correlates with symptom severity in Parkinson's disease. *Ann Neurol* 38, no. 4: 589-98.

Semchuk, K.M. , E.J. Love, and R.G. Lee. 1992. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology* 42: 1328-1335.

Serby, M., D. Moros, J. Rowan, L. Carlin, and M. Yahr. 1994. Maintenance ECT as adjunctive treatment to dopaminergic drugs in Parkinson's disease. *Biol Psychiatr* 35: 654.

Sies, H. and W. Stahl. 1998. Lycopene: antioxidant and biological effects and its bioavailability in the human. *Proc Soc Exp Biol Med* 218, no. 2: 121-4.

Stenfors, C., E. Theodorsson, and a. a. Mathé. 1989. Effect of repeated electroconvulsive treatment of regional concentrations of Tachkines, neurotensin, Vasoactive Intestinal Polypeptide, neuropeptide Y, and Galanin in rat brain. *J Neurosci Res* 24: 445-450.

Stern, M., E. Dulaney, S. Gruber, L. Golbe, M. Bergen, H. Hurtig, S. Gollomp, and P. Stolley. 1991. The epidemiology of Parkinson's Disease. A case-control study of Young-Onset and Old-Onset patients. *Arch Neurol* 48: 903-907.

Sutcliffe, R.L.G. and J.R. Meara. 1995. Parkinson's disease epidemiology in the Northampton District, England, 1992. *Acta Neurol Scand* 92: 443-450.

Svnilsson, E., A. Torvik, R. Lowe, and L. Leksell. 1960. Treatment of Parkinsonism by stereotactic thermolesions in the pallidal region: A clinical evaluation of 81 cases. *Acta Psychiatr Neurolo Scand* 35: 358-377.

Svenson, L. W. 1991. Regional disparities in the annual prevalence rates of Parkinson's disease in Canada. *Neuroepidemiology* 10, no. 4: 205-10.

Tandberg, Elise , Jan P. Larsen, Ernst G. Nessler, Trond Riise, and Johan A. Aarli. 1995. The Epidemiology of Parkinson's Disease in the County of Rogaland, Norway. *Movement Disorders* 10, no. 5: 541-549.

Tangney, C C and C M Tanner. 1993. Vitamin E and PD [letter]. *Neurology* 43: 634-635.

Tanner, C.M. , B. Chen, and W. Wang. 1989. Environmental factors and Parkinson's disease: a case-control study in China. *Neurology* 39: 660-664.

Tanner, 0C M, J A Cohen, B C Summerville, and C G Goetz. 1988. Vitamin use and Parkinson's disease [abstract]. *Ann Neurol* 23: 182.

Tanner, C.M., P. Grabler, and C.G. Goetz. 1990. Occupation and the risk of Parkinson's disease(PD): a case-control study in young-onset patients [abstract]. *Neurology* 40(suppl 1): 422.

Tanner, C.M., J.P. Hubble, and P. Chan. 1996. Epidemiology and genetics of Parkinson's disease. In *Movement Disorders. Neurologic principles and practice*, ed. R.L. Watts and W.C. Koller:137-152. New York: McGraw-Hill.

The-Parkinson-study-group. 1993. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 328: 176-183.

Tibbling, G., H. Link, and S. Öhman. 1977. Principles of albumin and IgG analyses in neurological disorders. I. Establishment of reference values. *Scand J Clin Lab Invest* 37: 385-390.

Tyler, Laurence Kenneth. 1992. A history of Parkinson's disease. In *Handbook of Parkinson's disease*, ed. William Koller:1-34. New York: Marcel Dekker, Inc.

Wahlstedt, Claes and markus Heilig. 1995. Neuropeptide Y and related peptides. In *Psychopharmacology: The fourth generation of progress*, ed. Floyd E. Bloom and David J. Kupfer:543-551. New York: Raven Press Ltd.

Wang, S. J., J. L. Fuh, C. Y. Liu, K. P. Lin, R. Chang, J. S. Yih, P. Chou, K. N. Lin, E. L. Teng, E. B. Larson, and et al. 1994. Parkinson's disease in Kin-Hu, Kinmen: a community survey by neurologists. *Neuroepidemiology* 13, no. 1-2: 69-74.

Wang, Y.S., Y.M. Shi, Z.Y. WU, Y.X. He, and B.Z. Zhang. 1991. Parkinson's disease in China. Coordinational Group of Neuroepidemiology, PLA. *Chin Med J* 104, no. 11: 960-964.

Ward, C., G. M. Stern, R. T. Pratt, and P. McKenna. 1980. Electroconvulsive therapy in parkinsonian patients with the "on-off" syndrome. *J Neural Transm* 49, no. 1-2: 133-5.

Webster, D. 1968. Clinical analysis of the disability in Parkinson's disease. *Mod Treatm* 5: 257-282.

- Weisburger, J. H. 1998. Evaluation of the evidence on the role of tomato products in disease prevention. *Proc Soc Exp Biol Med* 218, no. 2: 140-3.
- Wengel, S. P., W. J. Burke, R. F. Pfeiffer, W. H. Roccaforte, and S. R. Paige. 1998. Maintenance electroconvulsive therapy for intractable Parkinson's disease. *Am J Geriatr Psychiatry* 6, no. 3: 263-9.
- Wermuth, L., P. Joensen, N. Bungler, and B. Jeune. 1997. High prevalence of Parkinson's disease in the Faroe Islands. *Neurology* 49, no. 2: 426-32.
- Vieregge, P, C V Mararvic, and H-J Friedrich. 1992. Life-style and dietary factors early and late in Parkinson's disease. *Can J Neurol Sci* 19: 170-173.
- Wilder, J., G. L. Brown, and Z. M. Lebensohn. 1975. Letter: Parkinsonism, depression, and ECT. *Am J Psychiatry* 132, no. 10: 1083-4.
- Willett, Walter C. 1998. Nutritional Epidemiology. In *Modern Epidemiology*, ed. Kenneth J. Rothman and Sander Greenland:623-642. Philadelphia: Lippincot-Raven.
- Vitek, Jerrold L. 1996. Stereotaxic surgery and deep brain stimulation for Parkinson's disease and movement disorders. In *Movement Disorders Neurologic Principles and Practice*, ed. C.W. Koller and R.L. Watts:237-255. New York: McGraw-Hill.
- Young, B. K., R. Camicioli, and L. Ganzini. 1997. Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. *Drugs Aging* 10, no. 5: 367-83.
- Young, R. C., G. S. Alexopoulos, and C. A. Shamoian. 1985. Dissociation of motor response from mood and cognition in a parkinsonian patient treated with ECT. *Biol Psychiatry* 20, no. 5: 566-9.
- Yudofsky, S. C. 1979. Parkinson's disease, depression, and electroconvulsive therapy: a clinical and neurobiologic synthesis. *Compr Psychiatry* 20, no. 6: 579-81.
- Yudofsky, S. C. 1981. Electroconvulsive therapy in general hospital psychiatry: a focus on new indications and technologies. *Gen Hosp Psychiatry* 3, no. 4: 292-296.
- Zervas, Iannis and Max Fink. 1991. ECT for refractory Parkinson's disease. (Letter to the editor). *Convulsive Therapy* 7, no. 3: 222-223.
- Zervas, I. M. and M. Fink. 1992. ECT and delirium in Parkinson's disease [letter]. *Am J Psychiatry* 149, no. 12: 1758.
- Ziv, I. and E. Melamed. 1998. Role of apoptosis in the pathogenesis of Parkinson's disease: A novel therapeutic opportunity? [editorial]. *Mov Disord* 13, no. 6: 865-70.