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EPIDEMIOLOGY OF PARKINSON'S DISEASE

Caroline M. Tanner, MD, and Samuel M. Goldman, MD, MPH

This article reviews the epidemiology of Parkinson's disease (PD). The first section identifies terms and concepts important to the subsequent discussion. The next sections consider disease frequency and proposed risk factors. Etiologic theories resulting from these epidemiologic studies are discussed briefly.

DEFINITIONS

Parkinson's Disease

Parkinson's disease, a disorder of unknown cause, is a distinct clinical and neuropathologic entity, characterized clinically by bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment. Loss of pigmented neurons, most prominently in the substantia nigra, and presence of associated characteristic ubiquitin-positive cytoplasmic inclusion bodies (Lewy bodies, clear bodies) are the chief pathologic features. Parkinsonism of known cause and neurodegenerations with multiple system involvement or significant striatal lesions are excluded (such as progressive supranuclear palsy, olivopontocerebellar atrophy, Shy-Drager syndrome, multiple system atrophy, or striatonigral degeneration).[77]

Epidemiologic Terms

Incidence is the number of new cases of a disorder first developed or diagnosed during a specific time interval within a predefined population at risk. In contrast, *prevalence* refers to the total number of persons with the disorder at a fixed point in time. Prevalence is a function of both disease incidence and duration. Improved diagnostic capabilities can produce an apparent increase in

From The Parkinson's Institute, Sunnyvale, California

prevalence. Prolonged survival of persons with disease causes an actual increase in prevalence. Ideally, incidence and prevalence are determined by screening entire populations defined by specific geographic or political boundaries: *community- or population-based studies.*[127] Estimates of prevalence based on populations identified by other methods, such as participants in a hospital clinic, do not reflect accurately the general population of an area, as cultural, economic, or other factors may influence case selection *(selection bias).*

Investigations of risk factors for disease may be prospective or cross-sectional.[127] *Prospective cohort or follow-up studies* identify unaffected persons who differ with respect to a specific factor proposed to be related to the disease (an *exposure*). These individuals are observed over time, and the frequency of new disease in exposed and unexposed persons is determined. PD is an uncommon disorder beginning in late life. The latency from onset of neurodegeneration to onset of clinical signs is unknown. In such a situation, prospective cohort studies are problematic because a large number of unaffected individuals must be followed for decades. Cross-sectional methods, such as *case-control studies,* are faster and more economical. In case-control studies, individuals already affected with the disease of interest are compared to individuals without the illness, and exposures proposed to relate to the illness are compared. The retrospective nature of case-control studies makes them prone to *recall bias,* whereby cases have improved or altered recall of past exposures relative to controls, the result of heightened vigilance in association with the diagnosis of a chronic illness. Finally, in some cases (such as toxicant-induced parkinsonism), identification and intensive investigation of an unusually high incidence of disease, either in space or in time (a *cluster*), may provide important clues to disease etiology.

PROBLEMS ENCOUNTERED IN EPIDEMIOLOGIC STUDIES OF PARKINSON'S DISEASE

There is no antemortem diagnostic test for PD. Consequently, diagnostic accuracy is a challenge in epidemiologic studies of PD. The most reliable antemortem diagnostic method is expert neurologic examination. Although autopsy diagnosis is definitive, this long follow-up has not been possible in any published epidemiologic study of PD. Because differing diagnostic methods can result in differences in the persons studied, these methods should be reviewed critically in all epidemiologic studies of PD. For example, the level of expertise of the diagnosticians can affect diagnostic accuracy dramatically. In some communities, essential tremor accounted for 10% to 40% of the false-positive diagnoses of PD.[94, 104] Conversely, bona fide PD may be misdiagnosed as depression or, in the very elderly, "normal" aging. Neurodegenerative disorders, such as progressive supranuclear palsy or multiple system atrophy, may not be distinguished easily from PD early in the course of illness.[77]

Temporal differences in diagnostic practices also can limit comparability across studies. Many of the neurodegenerative disorders with multiple system involvement and parkinsonism generally were recognized only in the last several decades. These may have been included in earlier studies of PD. Some cases classified as arteriosclerotic parkinsonism in the past today might be considered typical PD.[15, 80, 93] In other reports, parkinsonism of known cause (drug-induced parkinsonism and postencephalitic parkinsonism) were grouped along with PD in determining incidence or prevalence rates.[15, 80, 116] Because these three types of parkinsonism are distinct, such a grouping could result in erroneous conclusions about disease patterns or risk factors.

FREQUENCY OF PARKINSON'S DISEASE

Incidence and Prevalence

James Parkinson's 1817 report of six cases[110] preceded the first community-based investigations of disease frequency by one and one half centuries. In 1958, Kurland[80] reported an estimated combined prevalence of 187 per 100,000 for postencephalitic, arteriosclerotic, and nonarteriosclerotic parkinsonism in the population of Rochester, Minnesota. Annual disease incidence was estimated to be 20 per 100,000 persons. Case identification was performed through the records linkage system of the Mayo Clinic. Those residents not seeking medical care would have been missed by this method. Because PD has significant associated disability, however, most cases were likely identified. In 1967, Gudmundsson[55] identified PD cases in Iceland by physicians' reports and personal examination, estimating a combined annual incidence of 16 per 100,000 cases for arteriosclerotic and nonarteriosclerotic parkinsonism. Estimated prevalence for these two disorders was 162 per 100,000, an estimate similar to that for Rochester, Minnesota. Numerous subsequent surveys have used variations on these methods with a variety of available health care records (e.g., national health registries; pharmacy rosters; hospital and chronic care facility rosters; questionnaires directed to physicians, nurses, and social workers.) to identify persons with PD.* All of these studies would have missed early cases and cases not receiving medical care.[103, 129] Pharmacy drug-sale rosters have been shown to overestimate PD prevalence, especially in women.[25] Diagnostic errors, therefore, could have caused increased or decreased inclusion of actual cases. Results from many of these are shown in Table 1.

A potentially more accurate method for determining disease frequency in a community involves a door-to-door survey of all households. Because such studies are time- and cost-intensive, often only those groups at higher risk of disease are studied. For example, only persons older than a certain age have been evaluated in surveys of populations interested in PD. Persons identified by a screening method as possibly suffering from a specific disorder then are referred for expert evaluation. Door-to-door surveys are costly, but a number of such surveys have been performed successfully, often in association with a national census.[1, 12, 87, 103, 123, 129, 130, 153] Results of these surveys are presented in Table 2.

Geographic Variation

Estimates of disease prevalence vary widely, from 31 per 100,000 in Libya[6] to 328 per 100,000 in the Parsi community in Bombay, India.[12] Although methodologic differences and population age distributions may explain some of this variation, even after adjusting for many of these inconsistencies, geographic prevalence differences persist.[160] Several North American studies also have found significant regional differences in prevalence, with a suggestion of northwest to southeast gradients in both Canada and the United States.[11, 84, 137] It is possible that different distributions of factors related to PD causes across populations may contribute to geographic differences in disease frequency. These

*References 6, 15, 28, 57, 67, 72, 94, 98, 104, 107, 116, 124, 136, 137, 145.

Table 1. INCIDENCE AND CRUDE PREVALENCE OF PARKINSON'S DISEASE IN COMMUNITY-BASED STUDIES

Location (Reference)	Publication Year	Prevalence (per 100,000)	Annual Incidence (per 100,000)
Rochester, MN (Kurland[80])	1958	187.0	20.0
Carlisle, England (Brewis et al[15])	1966	113.0	12.0
Victoria, Australia (Jenkins[67])	1966	85.0	—
Iceland (Gudmundsson[55])	1967	162.0	16.0
Baltimore, MD (Kessler[72])	1972	128.0*	—
Turku, Finland (Marttila & Rinne[94])	1976	120.1	15.0
Aberdeen, Scotland (Mutch et al[104])	1986	164.2	—
San Marino (D'Alessandro et al[28])	1987	152.0	—
Yonago, Japan (Harada et al[57])	1983	80.6	10.0
Sardinia, Italy (Rosati et al[124])	1980	65.6	4.9
Northampton, United Kingdom (Sutcliffe et al[136])	1985	108.4	—
Benghazi, Libya (Ashok et al[6])	1986	31.4	4.5
Rochester, MN (Rajput et al[116])	1987	—	20.5
Izumo City, Japan (Okada et al[107])	1990	82.0	—
Ferrara, Italy (Granieri et al[54])	1991	164.7	10.0
New York, NY (Mayeux et al[98])	1992	99.4	—
Dunedin, New Zealand (Caradoc-Davies et al[20])	1992	110.4	—
Alberta, Canada (Svenson et al[137])	1993	244.4	—

*Male patients.

factors could include genetic differences in susceptibility to disease, differences in exposure to causative factors, and differences in exposure to protective factors.

Temporal Variation

A number of studies have attempted to look at changes in the frequency of PD over time, searching for temporal patterns that could provide important etiologic clues. For example, an increasing incidence over time that correlates with the industrialization of a region could implicate industrial chemicals or

Table 2. PARKINSON'S DISEASE CRUDE PREVALENCE IN DOOR-TO-DOOR SURVEYS

Location (Reference)	Publication Year	Ages Screened (Years)	Prevalence (per 100,000)
Chinese cities (Li et al[87])	1985	>50	44.0
Copiah Co, MS (Schoenberg et al[129])	1985	>39	347.0
Igbo-ora, Nigeria (Schoenberg et al[130])	1988	>39	58.6
Parsi community, Bombay, India (Bharucha et al[12])	1988	All	328.3
Vejer de la Fontera, Cadiz, Spain (Acosta et al[1])	1989	All	270.0
Terrasini, Santa Teresa di Riva, Sicily, Italy (Rocca et al[123])	1990	All	243.0
Sicily, Italy (Morgante et al[103])	1992	>12	257.2
Kin-Hu, Kinmen, China (Wang et al[153])	1994	>50	170.0

related lifestyle changes as risk factors. Similarly, periodic fluctuation in incidence might suggest an infectious etiology.

A review of Olmstead County data found no significant change in PD incidence over the relatively brief period from 1967 through 1979.[117] Zhang et al[160] reviewed a number of incidence studies, age adjusting them to a single population, and detected no change in incidence rates over the past 50 years. Changes in disease frequency over long periods, however, are very difficult to measure reliably because of changes in and inconsistent application of diagnostic criteria. Additionally, many studies rely on death record analysis for ascertaining cases, introducing great variability owing to the inconsistent reporting of PD as a cause of death. Their shortcomings acknowledged, these studies show consistent dramatic changes in PD-related mortality. During the past 2 to 3 decades, irrespective of geographic location, death rates have fallen for those younger than age 65 and increased in those older than age 75.[24, 26, 64, 83, 146, 150] These observations are compatible with improved survival due to levodopa therapy, with mean age at death increasing approximately 5 years during the past 20 years.[83, 149]

Changes in PD incidence and mortality (after adjustment for population aging) could reflect improved diagnosis or improved record-keeping, or might reflect relative changes in mortality from other competing diseases, such as stroke and heart disease.[121, 122]

RISK FACTORS FOR PARKINSON'S DISEASE

Age

Increasing age is the only unequivocal risk factor for PD. PD incidence increases with increasing age throughout the life span.[116] This is true in all community-based studies, regardless of the absolute prevalence of disease in

the population.[20, 57, 80, 94, 98, 103, 104, 124, 136] Some examples of age-specific prevalence in different communities are shown in Figure 1. The reasons for this relationship are not known. Possible explanations for the near exponential correlation between increasing age and PD prevalence include age-related neuronal vulnerability or a causal mechanism dependent on the passage of time.

Because of the strength and consistency of this risk factor, comparisons of disease frequency among populations must be adjusted for their differing age distributions.[160] One would expect crude (unadjusted) PD incidence and prevalence to be higher in a community with a greater proportion of elderly individuals. Similarly, evaluation of any putative risk factor requires concomitant adjustment for the distribution of that risk factor with respect to age.

Gender

Because of their greater longevity, women constitute an increasing percentage of the population as age increases. For this reason, if risk is equal, one would expect the crude prevalence of PD to be greater in women. Age-adjusted or age-specific prevalences are more useful statistics for understanding potential causes of PD (i.e., at a given age, what is the likelihood that an individual will have PD?). Although by no means a universal finding, an increasing percentage of studies find men to have a modestly increased age-adjusted PD prevalence.* This trend also persists across races,[64, 83, 89, 98] particularly in China, where the male-to-female ratio ranges from 2.4 to 3.7.[23, 87, 140, 153] Examples of age-adjusted prevalence ratios by gender are shown in Table 3. Whether the increased preva-

*References 6, 23, 28, 57, 67, 72, 87, 89, 94, 98, 117, 124, 136, 137, 140, 153.

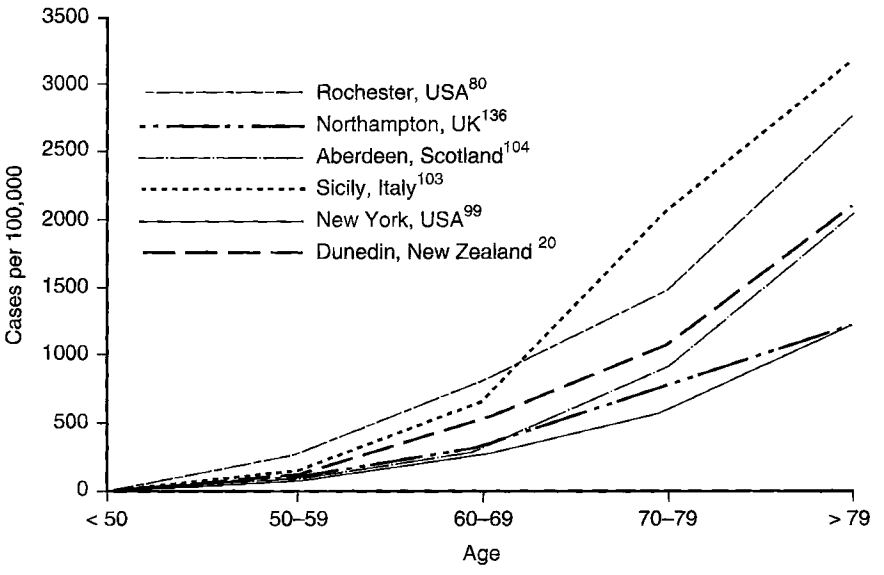

Figure 1. Parkinson's disease age-specific prevalence.

Table 3. PARKINSON'S DISEASE: GENDER RATIO OF AGE-ADJUSTED PREVALENCE

Location (Reference)	Male-to-Female Ratio
San Marino (D'Alessandro et al[28])	1.24
Yonago, Japan (Harada et al[57])	0.86
Chinese cities (Li et al[87])	3.70
Sardinia, Italy (Rosati et al[124])	1.38
Northampton, United Kingdom (Sutcliffe et al[136])	1.30
Finland (Marttila & Rinne[94])	0.98
Benghazi, Libya (Ashok et al[6])	1.04
Rochester, MN (Rajput et al[117])	1.48
Alberta, Canada (Svenson et al[137])	1.20
New York, NY (Mayeux et al[98])	1.73
Denmark (Kurtzke et al[83])	1.79*
Japan (Imaizumi & Kaneko[64])	1.29*

*Mortality data.

lence in men is a function of biology or of male-related lifestyle factors is not clear. Further investigation of factors underlying these foci of increased male prevalence may provide important clues to the cause of PD.

Race

PD prevalence generally appears to be highest in Europe and North America, whereas rates in Japan, China, and Africa are markedly lower (see Tables 1 and 2). Similarly, one community-based[98] and several hospital-based series in the United States and Africa found PD prevalence to be much lower among blacks.[71, 108, 109] These observations suggest that there is a greater risk for PD among whites. Other differences among the populations studied, however, such as underlying age distribution and use of medical care, also could cause such differences in prevalence. Exceptions to the above findings are two door-to-door studies—one performed in Copiah County, Mississippi,[130] and the other in a Parsi colony in Bombay, India.[12] Prevalence in Copiah County was similar between whites and blacks, if cases were chosen using the least stringent diagnostic criteria (i.e., possible Parkinson's disease), although whites continued to have higher prevalence if more rigorous criteria (i.e., probable Parkinson's disease) were used to identify cases. In the Parsi community in Bombay, prevalence was similar to that found in Europe and North America. The Parsis are Persian

descendants who migrated to India between the seventh and tenth centuries. They formed a closed community into which conversion is impossible. These facts may account for the high prevalence observed, despite their Asian residence.

Although socioeconomic or environmental factors may explain the prevalence differences cited here, a still-to-be-refuted possibility is that PD is more common in whites, most likely as the result of a common genetic characteristic.

Genetic Predisposition

Heredity is another commonly identified risk factor for PD. First, many examples of familial parkinsonism have been reported. Several kindreds with multiple members with apparent autosomal-dominant parkinsonism have been described,[33] but most of these studies are limited by their reliance on family-derived histories for deceased relatives. In addition, the clinical and pathologic features of the majority of described kindreds are not fully consistent with those of typical PD.[34, 50, 100, 125, 156]

Maraganore et al[91] studied the first-degree relatives of 20 British PD patients who reported at least one additional family member with PD. Examination-verified idiopathic PD indistinguishable from sporadic PD was found in 13 of 69 living first-degree relatives, leading the authors to propose an autosomal-dominant pattern of inheritance with reduced penetrance. Payami et al[112] studied PD frequency in 586 first-degree relatives of 114 PD patients ascertained from a movement disorder clinic and in a similar number of controls. All affected relatives had been diagnosed by a community physician. Relatives of PD patients were 3.5 times more likely to have PD than relatives of controls, again suggesting an autosomal-dominant pattern. Notwithstanding their possible significance, it must be emphasized that neither of these studies used population-based methods, and it cannot be assumed that these findings are generalizable to the population at large. Additionally, these studies assess the probability of a positive family history of PD given that the proband has PD, when the real question regards the probability of PD given a positive family history.

Other studies support a less prominent role for genetic factors, postulating multifactorial inheritance with symptoms dependent on environmental factors.[7, 79, 93, 101] Twin studies further support a less prominent contribution of genetic factors in PD, as concordance rates between monozygotic and dizygotic twins are similar.[92, 96, 151, 152, 155, 161] In classic autosomal-dominant disorders, monozygotic twins show much higher concordance than do dizygotic twins. PD, however, is a disorder of late life. If onset age differs significantly between twins, and one twin dies before symptoms are apparent, genetically concordant twins may appear to be discordant. A recent positron emission tomography (PET) scan study by Burn et al[18] supports this possibility. They looked at putamenal ^{18}F-dopa uptake in twin pairs discordant for PD clinically and found that 30% to 40% of asymptomatic cotwins had significantly decreased uptake. Similar PET scan results were reported recently by Piccini et al.[113] Concordance rates for decreased ^{18}F-dopa uptake, however, did not differ for monozygotic and dizygotic twins, arguing against a classic Mendelian autosomal-dominant cause of this observation. Moreover, the relationship between this radiographic finding and subsequent clinically or pathologically diagnosed PD is unknown. Neither is the population prevalence of decreased putamenal ^{18}F-dopa uptake well understood. Prospective observation of these and other cases will be useful in determining the significance of these interesting findings.

Consistent with multifactorial theories of PD etiology, several genes that code for metabolic enzymes have been identified that may contribute to PD risk. Variant alleles for cytochrome P450 isoenzyme CYP2D6,[2, 5, 78, 132, 147] and several specific monoamine oxidase haplotypes[61, 82] occur with increased frequency in individuals with PD, although these associations are not reported universally.[81] These variants potentially could result in toxic effects from levels of some endogenous or exogenous compounds that might not otherwise be toxic (i.e., *gene-environment interaction*).

It is hoped that the role of genetic factors in PD etiology will be clarified soon, as the rapid development of molecular genetic technology has focused much attention on this question.

Toxicant Exposure

The idea that exposure to an exogenous agent might cause PD was triggered by the observation of a cluster of parkinsonism caused by the intravenous injection of the compound 1-methyl-1,2,4,6-tetrahydropyridine (MPTP) by narcotics addicts.[85] Prior to this discovery, parkinsonism was known to result from numerous chemical injuries,[46] but MPTP-induced parkinsonism is remarkable in that it strictly mimics the anatomic and clinical features of PD rather than causing more widespread CNS injury. This observation sparked a search for naturally occurring environmental factors that might be causally related to idiopathic PD. One key aspect to the search for environmental causes of PD, in contrast to MPTP, is that signs of idiopathic PD develop very gradually. Substances that are mildly toxic, or which ingress or accumulate in the brain slowly, are difficult to evaluate, and their significance could be missed.[144]

International differences in PD prevalence could be explained by international differences in toxicant exposure. PD appears to be less common in countries more recently industrialized. Studies using antiparkinsonian drug sales to estimate prevalence found vegetable farming, wood pulp mills, and steel alloy industries in areas with the highest disease prevalence.[4, 7] Very similar results were found in a Michigan ecologic study using county-specific PD mortality rates,[126] where significantly higher rates were found in counties with paper-, chemical-, iron-, or copper-related industries.

Rajput et al[118] found an association between young age at PD onset and residence in rural Saskatchewan, and Tanner et al[141] found a similar association in a Chicago-based clinical series. These observations have been tested in numerous case-control and ecologic studies.* Many of these are summarized in Table 4. Although both the methods used and the locations of these studies have differed, all show an association between at least one of the proposed exposures—rural residence, farming, well water drinking, or herbicide/pesticide exposure—and an increased risk for developing PD. Hubble et al[63] used a multiple logistic regression model to discern that most of the associations they observed were in fact a function of their relationship to pesticide use.

The structural and mechanistic resemblance of some common agricultural chemicals to the toxin MPTP[3, 106, 119] is particularly intriguing. The significance of these associations should be weighed cautiously, however. All of the studies previously described are limited by small size, and differing methods prevent direct comparisons. Although reproducibility of the associations over many

*References 19, 29, 32, 54, 58–60, 63, 69, 77, 102, 126, 131, 135, 137, 138, 140, 154.

Table 4. CASE-CONTROL STUDIES TESTING THE ASSOCIATION BETWEEN RURAL LIFE, AGRICULTURAL CHEMICALS, OR WELL-WATER DRINKING AND PARKINSON'S DISEASE

Location (Reference)	No. Cases/ No. Controls	Rural Home	Farming	Well-water Drinking	Herbicides/ Pesticides
China (Tanner et al[140])	100/200	−	−	−	+
Quebec (Zayed et al[159])	42/84	NA	−	+	+
Madrid (Jimenez-Jimenez et al[69])	81/162	NA	NA	+	+
Kansas (Koller[77])	150/150	+	+	+	−
Hong Kong (Ho et al[60])	35/105	+	+	+	+
Chicago† (Tanner et al[138])	78/78	−	+	−	−
British Columbia (Hertzman et al[58])	57/122	NA	NA	−	+
New Jersey/Pennsylvania† (Dulaney et al[32])	154/154	+*	NA	−	−
Campania, Italy (Campanella et al[19])	83/83	NA	NA	+	NA
California, 7th Day Adventists (Davanipour et al[29])	49/>34,000	+	NA	NA	NA
Kansas (Wong et al[158])	38/38	+	−	+	−
Calgary (Semchuk et al[131])	130/260	−	+	−	+
Spain (Morano et al[102])	74/148	+	−	+	+*

*$p = 0.06$.
†Parkinson's disease onset <51 y.
+ = significant positive association; − = no association; NA = not assessed.

different studies lends strength to the observations, a cause/effect relationship cannot be assumed. Much further collaborative work between clinicians, epidemiologists, and laboratory scientists is necessary to clarify the import of the association between rural residence or its associated factors and PD.

Infection

The observation that parkinsonism was a common late sequela of encephalitis lethargica, a disorder that was pandemic in the second and third decades of this century, prompted the postulate that all cases of parkinsonism were the result of exposure to that infectious agent.[114] The corollary prediction that PD ultimately would disappear now has been proved incorrect as survivors of that epoch died, and few cases of parkinsonism today are thought to be postencephalitic. One study[97] suggested that in utero exposure to influenza virus may cause a loss of nigral neurons and consequent increased vulnerability to PD, but this observation was not confirmed.[35]

Many attempts to identify an infectious agent in PD failed.[36, 95, 154] Fazzini et

al[41] found increased cerebral spinal fluid (CSF) antibody titers to coronaviruses in persons with PD. Specific coronaviruses have an affinity for basal ganglia in some animals, and members of this species commonly affect agricultural animals such as pigs. Hubble et al[62] and Kohbata et al[75] found increased *Nocardia* antibody titers in PD patients, and *Nocardia* can cause a levodopa-responsive movement disorder in mice associated with its specific affinity for substantia nigral neurons.[10, 74] Rather than reflecting an exposure to an environmental chemical, the increased risk of developing PD associated with rural residence may reflect environmental exposure to an infectious agent.

Trauma

Retrospective case-control studies often report an association between head trauma and PD.[13, 32, 38, 135, 141] Studies comparing prospectively collected information (that is, information collected before the person got PD), however, do not find this association.[117, 157] Patients with a chronic illness typically seek explanations for their disease in prior experiences, and those with CNS injuries might be particularly thoughtful about head injuries. A similar pattern of recall is seen in other neurologic diseases, such as Alzheimer's disease, in which prospectively collected information shows no association between head injury and disease, but retrospectively collected information typically suggests that head trauma is associated with Alzheimer's disease.[21] It is most likely that the reported association between head trauma and PD reflects biased recall, rather than a cause/effect association. Consistent with this conclusion, Goetz et al[47] in 1991 found that PD patients who sustain head trauma have no change in the long-term course of their disease. Unless prospectively collected information shows such an association, trauma should not be considered to increase the risk for PD.

Emotional Stress

Both Charcot[22] and Gowers[52] cited stress as a possible cause of PD. Laboratory studies suggest that stress-produced changes in central dopamine systems theoretically could contribute to the development of parkinsonism.[133, 134] Similarly, persons already affected with PD experience transient worsening of their symptoms during stressful periods.[45] Two reports linked the extreme emotional and physical hardship of concentration camp imprisonment with the subsequent development of PD.[43, 146] Whether these observations reflect an accelerated nigral injury as the result of stress-related increase in dopamine turnover with resultant increased oxidative injury, nutritional deficiencies of dietary protective agents, or other factors cannot be determined. Evaluation of the relationship of less severe emotional or physical stress to the development of PD poses a methodologic challenge.

PROTECTIVE FACTORS FOR PARKINSON'S DISEASE

Diet

Oxidative mechanisms have been proposed to be involved in the pathogenesis of PD, and, in consequence, intake of antioxidant vitamins has been proposed to protect against the development of PD.[17, 27, 40] Patients with vitamin E defi-

ciency show reduced putamenal ^{18}F-dopa uptake in PET scans,[30] although no differences have been found in serum[42] or in brain tocopherol levels[31] in patients with PD. Consumption of foods rich in tocopherol decreased the risk of developing PD in two case-control studies, one comparing PD cases to same-sex siblings and one comparing subjects to spouses.[48, 51] The use of supplemental multivitamins, vitamin E, or cod liver oil was associated similarly with a decreased risk for PD,[142] although the ability of vitamin E supplements to slow progression of already diagnosed PD is inconclusive.[39, 86] No significant differences between cases and controls in dietary intake of vitamins E or C, beta-carotene, protein calories, or total calories were found in a Chinese population,[139] but the tocopherol content of many of the foods commonly eaten in China was not available, so this negative result simply could reflect inadequate information.

Although the numbers studied to date are small, these studies suggest that eating foods rich in tocopherol or some associated behavioral or dietary factors may protect against the development of PD in some cases. These observations allow the suggestion that areas with a low prevalence of PD may not be those with a lesser concentration of environmental toxins but rather those in which there is higher dietary intake of protective substances or a lower dietary intake of pro-oxidants. This latter possibility is supported by a recent case-control study that found increased animal fat intake in PD cases relative to controls.[90]

Cigarette Smoking

A study of US military veterans in the late 1960s resulted in the observation of an inverse association between smoking and PD.[70] The low prevalence of cigarette smoking among prevalent cases of PD is an observation confirmed in numerous subsequent case-control studies in the United States and Europe,[9, 13, 16, 32, 44, 56, 68, 73, 105, 143, 154] and recently in a large prospective study in Hawaii, where a modest dose–response relationship was observed.[53] Most of these studies found an odds ratio of approximately 0.5 for ever-versus-never having smoked. Five studies, however, found no association between smoking and PD.[14, 60, 99, 118, 140] Two of these studies, performed in China or Hong Kong, raise questions concerning any protective effect of cigarette smoking. Smoking is extremely rare among Chinese women but relatively common among men, but PD occurs in Chinese men nearly four times more often than in Chinese women.[87, 140] If smoking exerted a true biologic protective effect, a higher prevalence of PD would be expected in the nonsmoking Chinese women than in men.

The proposed protective effect of cigarette smoking could be confounded by many factors, including a greater propensity for persons to quit smoking because they are becoming ill even before being diagnosed[99] and the possibility that patients with PD who smoke have greater mortality than those patients who do not smoke.[37, 120] Rather than reflecting an actual biologic action, decreased smoking in PD simply could reflect the more conservative personality that may accompany PD[13, 48, 111] (i.e., smoking behavior could be a reflection of an underlying process, rather than the cause of that process). Nonetheless, given the consistency and strength of the inverse association and the suggestion of a dose–response relationship in a large prospective study, the bulk of epidemiologic evidence supports a potentially protective effect of cigarette smoking on PD risk. Coupled with studies demonstrating protective effects of nicotine on age-, transection-, and MPTP-induced dopaminergic neuronal cell loss in rodent substantia nigra,[65, 66, 115] the evidence further supports the possible protective role of smoking on PD risk.

SUMMARY

The epidemiologic studies reviewed here have provided insights into the etiology of PD. Evidence increasingly suggests that, like many other chronic age-related diseases, PD is a multifactorial disorder, with both genes and environment contributing to risk. As the elderly population of the world grows, incidence and prevalence of PD will continue to increase, underscoring the importance of further delineating risk factors. The introduction of levodopa and other pharmacologic therapies over the last 2 decades has postponed disease morbidity and mortality, but morbidity and mortality still are increased markedly relative to unaffected individuals. The development of therapies that may slow disease progression makes early identification and treatment of PD particularly important. Investigations of early markers of PD, or markers of disease susceptibility, are critical areas for future research. These efforts all will be aided by careful collaboration between epidemiologists and laboratory scientists.

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Address reprint requests to

Caroline M. Tanner, MD
The Parkinson's Institute
1170 Morse Avenue
Sunnyvale, CA 94089