Objective: To evaluate whether the survival of patients with Parkinson disease (PD) is shorter than that of the general population.

Design: Survival was investigated in a cohort of patients with PD previously identified during a population-based prevalence study (prevalence day, November 1, 1987; reference follow-up date, October 31, 1995). The survival of patients with PD was compared with that of a control sample randomly selected from the same population (2 controls for each case, matched for age, sex, and study municipality). The causes of death in the 2 groups were also compared. Both univariate and multivariate survival analyses were performed to investigate the association with disease-related variables.

Setting: A door-to-door 2-phase prevalence survey performed in 3 Sicilian municipalities.

Patients: Fifty-nine patients with PD and 118 controls.

Results: Patients with PD showed a high risk of death (relative risk, 2.3; 95% confidence interval, 1.60-3.39). Greater age at November 1, 1987, high Hoehn-Yahr score, and lack of levodopa therapy were associated with a lower survival on univariate analysis. Multivariate analysis confirmed the association between shorter survival among patients with PD and greater age on November 1, 1987. One-way analysis of variance indicated a different effect of levodopa therapy according to age. Multivariate analysis did not confirm this finding. Pneumonia was the cause of death most frequently associated with PD.

Conclusion: This study indicates that patients with PD have a shorter survival time than the general population.

Arch Neurol. 2000;57:507-512

Before the introduction of levodopa in the therapy of Parkinson disease (PD), many clinical and epidemiological reports showed that patients with PD had a shorter survival than the general population.1 Hoehn and Yahr,2 in their leading article, reported a mortality ratio 2.9 times higher than that of the general population adjusted for age, sex, and race.

Since the middle 1970s, various studies, mostly based on case series and using comparative routine mortality statistics, have reported either a consistent reduction of mortality for PD or similar survival curves for patients with PD and the general population.3 In these articles, the increased survival of patients with PD was correlated with the introduction of levodopa therapy. Articles showing a more rapid progression of the disease in patients who delayed starting levodopa therapy corroborated this view.4,5 Moreover, 2 population-based surveys, performed in Rochester, Minn,6 and in Olmsted County, Minnesota,7 showed that the survival time was significantly lower in patients with PD compared with the general population, but patients treated with levodopa had a survival similar to that of their referral population.

In contrast, most of the recent population-based surveys reported that patients with PD continue to survive for a shorter time than the general population, despite the introduction of levodopa therapy.8-11

The first aim of this study was to determine whether survival of patients with PD in a given Sicilian population is comparable with that of the general population. The second aim was to find out what demographic or clinical features influence survival. The last aim was to study the causes of death among patients with PD.

Results

Of the original 63 patients with idiopathic PD identified during the prevalence survey,12 we included 59 patients in this survival study. The remaining 4 patients were excluded from the study because 2 were not traced and 2 were judged at the rescreening not to be affected by idi-
PATIENTS AND METHODS

CASES

We considered all patients with idiopathic PD identified during a door-to-door prevalence survey conducted previously in Sicily, as part of a large-scale epidemiological survey of neurological diseases (the Sicilian Neuroepidemiologic Study).21-24 The Sicilian Neuroepidemiologic Study also evaluated the prevalence of PD and other types of parkinsonism in persons residing as of November 1, 1987, in any of 3 municipalities: Riposto (Catania province), Santa Teresa di Riva (Messina province), and Terrasini (Palermo province). The general method of the prevalence survey has been reported elsewhere.21-24 The study covered 24,496 subjects. Cases of parkinsonism were ascertained through a door-to-door 2-phase approach. The first phase was based on the administration of a brief screening instrument that included a symptom questionnaire and some simple tasks; it was performed by medically trained interviewers. In the second phase, study neurologists (G. Salemi, A.E., and F.P.) used specified diagnostic criteria to evaluate persons who screened positive. Diagnoses were reviewed by the local senior neurologist (L.M., G. Savettieri, and A.R.) for each municipality. To increase reliability across centers, diagnoses were discussed and adjudicated by a study panel. A diagnosis of parkinsonism required the presence of at least 2 of 4 cardinal signs (rigidity, resting tremor, bradykinesia, and impaired postural reflexes) in a person not receiving antiparkinsonian therapy or at least 1 sign in a specifically treated patient. The validity of these criteria for epidemiological purposes was confirmed recently.25 Idiopathic PD was defined by excluding other causes of parkinsonism through medical history information and direct patient examination. Specified diagnostic criteria for parkinsonism are detailed elsewhere.24

CONTROLS

To evaluate the survival of the general population, 2 controls for each case were selected among all residents included in the Sicilian survey and found to be free of parkinsonism.23,24 The population controls were matched by sex, age, and municipality to each case included in the study. When more than 2 potential controls were available for a given case, 2 of them were selected by means of a table of random numbers.

DATA COLLECTION

All the cases of idiopathic PD and the matched controls were contacted at the end of 1995 to evaluate their health status. The rescreening included a clinical evaluation and physical and neurological examination. Death certificates were obtained for persons who died before the day of last follow-up (October 31, 1995) to verify the date of death and all the causes of death.

DATA ANALYSIS

Relative risk (RR) was used to compare the risk of death among patients with PD and controls. To determine statistical significance, we used 95% confidence intervals and the χ² test with continuity correction. Survival was examined with Kaplan-Meier plots.26 The log rank test was used to evaluate the influence on survival of the selected variables in univariate analysis.27 A backward stepwise Cox proportional hazards model was used in a multivariate analysis to estimate RR for the main outcome measure (death).28 Influence on survival was evaluated for the following variables: sex; age at November 1, 1987 (categorical variable, ≤75 years and >75 years, for the univariate analysis; continuous variable for the multivariate analysis); interval between onset of the disease and November 1, 1987 (≤3 years and >3 years); diagnosis of PD formulated before the prevalence study or by the Sicilian Neuroepidemiologic Study investigators (old cases and new cases); stage of the disease at the time of the prevalence study, according to the Hoehn-Yahr scale (categorical variable, ≤2 and >2 score points, for the univariate analysis; Hoehn-Yahr score value for the multivariate analysis); municipality of origin, with 3 categories corresponding to the 3 municipalities studied during the prevalence survey; and levodopa intake at the time of the prevalence study, with 2 categories: medicated and unmedicated. The starting date for the survival analysis was the date of enrollment in the prevalence study rather than the date of onset of PD. This time is a more appropriate variable, because subjects may not recall the exact date of onset of the symptoms, especially if the symptoms are slight or difficult to label or identify.

The effect of therapy with levodopa on survival was further investigated by analyzing the survival of both patients and controls by stratifying for age at November 1, 1987. For this purpose, t test for independent samples, 1-way analysis of variance with Bonferroni correction, and multivariate analysis based on a Cox proportional hazards model adding an interaction term (age × medication) were used.

Differences in the cause of death between patients with PD and controls were evaluated by comparing RR. Fisher exact test, 95% confidence intervals, and χ² test with continuity correction were used to determine statistical significance. All analyses were performed with the statistical package SPSS.29

idiopathic PD. Data were also obtained for all the 118 matched controls.

Thirty-three (56%) of the 59 patients were female. The median age of patients with PD as of November 1, 1987, was 74 years (range, 50-89 years). The median age at November 1, 1987, was 74 years (range, 56-89 years) for men and 73 years (range, 50-87 years) for women.

At October 31, 1995, 35 patients (59%) and 30 controls (25.4%) were dead. The median survival was 73 months (range, 3-95 months) for patients with PD and 84.5 months (range, 8-96 months) for controls. The RR was 2.3 (95% confidence interval, 1.60-3.39). Figure 1 shows the Kaplan-Meier survival curves; a highly significant difference was found by comparing the survival of cases and controls (P < .001). A survival of 43 months was observed in 74% of patients with PD, while a survival of 96 months was observed for the same cumulative percentage of controls.
Table 1 reports the results of the univariate analysis for the selected variables. The survival of patients with PD was associated with age at November 1, 1987; Hoehn-Yahr score; and levodopa intake. Figure 2 shows the cumulative survival probability of patients with PD according to age at November 1, 1987 (A and B); levodopa therapy (C and D); and Hoehn-Yahr score at November 1, 1987 (E and F).

When we evaluated the influence on survival of all the selected variables, using a Cox proportional hazards multivariate analysis in a backward stepwise model, only age at November 1, 1987, maintained its statistical significance (Table 1).

Hypothesizing an age-related effect of levodopa on survival, we performed further statistical analyses to verify this hypothesis. Table 2 shows the results of the t test for independent samples and of 1-way univariate analysis obtained by comparing the survival time of patients medicated with levodopa with that of unmedicated patients and that of controls, stratifying by age at November 1, 1987 (50-69 years vs 70-89 years). These results suggest a different effect of levodopa therapy according to age. To confirm this result, we performed a Cox proportional hazards multivariate analysis adding an interaction term (age × medication). The interaction was not significant (P = .81). Finally, we performed the same analysis after stratification by age (50-69 years vs 70-89 years). The interaction term age × medication was not significant in both strata (50-69 years, P = .06; 70-89 years, P = .70); in the group aged less than 70 years, the interaction term was near significance. Our study probably did not have enough power to look at interaction with the Cox proportional hazards model.

Median age at death was 81.0 years for patients with PD (range, 57-94 years) and 82.5 years for controls (range, 69-93 years). The most frequent cause of death among patients with PD was heart disease (29%), which was also much more frequent in the control group (43%).

Table 3 shows the RR for the principal causes of death as reported in the death certificate. Pneumonia was the cause of death significantly associated with PD.

**COMMENT**

The most suitable approach to designing a survival study is that based on the follow-up of incident cases recruited...
during a population-based study. Such a study design is expensive and time-consuming. To our knowledge, only 1 study has been performed according to this design. This investigation evaluated the incidence and mortality of PD in a cohort of subjects, previously selected in the Hawaiian Islands during a survey on heart diseases. The mortality of patients with PD was higher than that in the general population and appeared to be associated with older age and longer disease duration. The association of mortality with levodopa therapy was not evaluated.
The present study was designed as a follow-up of a cohort of patients with PD previously identified during a door-to-door prevalence survey. Our case finding procedure therefore has its own methodological strength and weakness. The main weakness comes from its using prevalent cases, which causes the loss from the analysis of the more severe PD cases that do not survive until the prevalence day, and of male patients, who have a lower survival than female patients.

A second weakness is the limited size of the sample, which reduces the power of the study, particularly as regards the stratified analyses of survival variables; we reduced the impact of this limitation by matching 2 healthy controls to each patient.

The main strength of our study is the overall makeup of our sample, which was not constituted by a selection from an unrepresentative cohort of patients but came from the entire population of a well-defined community.

The present study shows decreased survival and a high mortality rate among patients with PD compared with their referral population. Both results are consistent with most population-based surveys that compare mortality among patients with PD with relevant matched controls.13-20 In contrast, studies based on case series found low mortality rates.1,2 However, this last methodological approach could introduce a serious selection bias if the recruitment of patients from a geographic region is not exhaustive. In addition, comparative routine statistics are the source of survival data for the general population in these studies; the trend of mortality statistics based on national data cannot follow the pattern of mortality in a limited geographic area. Finally, some of these studies were limited to only 3 years of follow-up.1,7,9 A longer follow-up makes it possible to observe an increase of mortality among patients with PD.30

The present survey shows that the age at death of patients with PD is consistently higher than that reported in older studies.1,4 The inclusion of prevalent cases of PD could partly explain this result.

Age at recruitment is the only variable that, at multivariate analysis, demonstrates an effect on PD survival. This issue is debated. Hoehn and Yahr2 suggested that the higher mortality observed among older patients could be largely attributable to a higher death rate in the older population. Our analyses do not fit with this hypothesis. We observed that survival was lower in older patients than in matched controls of the same age group. A possible determinant of mortality in PD is dementia.17 Dementia is associated with PD and mortality. Dementia is therefore a potential confounder, especially in the older age group where the incidence is the highest. Our study was designed to investigate several neurological disorders, but it did not assess dementia. The effect of age on mortality could be partially explained by the confounding effect of dementia.

Concerning levodopa therapy, various surveys5,17,19 indicated that it might improve the quality of life and survival of patients with PD during the early years of therapy only.30 On the contrary, several studies conducted in neurological centers5,6,11,12 and 2 population-based surveys, one performed in Rochester18 and the second performed among the population of Olmsted County with the use of incident cases,14 found that patients treated with levodopa showed a survival similar to that of their referral population. Our data suggest an age-related effect of levodopa therapy on survival. The survival time increases when levodopa treatment is initiated at younger ages; this “protective” effect is lost in older patients. However, one limitation of our study was the small sample size and therefore the inadequate power of the study to look at interactions with multivariate analysis. The heterogeneity of the effect of levodopa therapy across different age groups needs to be investigated further.

At univariate analysis, a high Hoehn-Yahr score proved to be associated with lower survival. This find-

### Table 2. Effect of Levodopa Therapy on Survival of Patients With Parkinson Disease

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No. of Subjects</th>
<th>Mean (SD) Survival, mo*</th>
<th>F Ratio F Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-69</td>
<td>7</td>
<td>87.4 (7.8)</td>
<td></td>
</tr>
<tr>
<td>70-89</td>
<td>17</td>
<td>55.1 (27.7)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Common Causes of Death Among Patients With Parkinson Disease and Controls

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Deaths</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cachexia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
<td>6.00† (1.69-21.34)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>2.29 (0.87-6.00)</td>
</tr>
<tr>
<td>Heart diseases</td>
<td>10</td>
<td>1.65 (0.62-3.30)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>2</td>
<td>1.33 (0.23-7.76)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Yates-corrected $\chi^2$ analysis was used for stroke and heart diseases, and Fisher exact test for cachexia, pneumonia, and malignant neoplasm.
†Bonferroni correction indicates that group C differs from the 2 others with P = .05.
ing is consistent with those of other studies.2,10,12,13 The association does not persist, however, after multivariate analysis.

During our prevalence survey,24 we found that 22 of the 63 patients with PD had never been diagnosed before. This variable does not influence the survival of patients with PD. This finding, which might appear surprising, could actually result from the fact that the newly diagnosed patients were those with later onset.24

Routine mortality statistics report longer survival in women than in men. It has been speculated that the similarity of survival curves between sexes in patients with PD may indicate a worse prognosis for women.4,10 Other surveys reported a higher mortality among women.2,20 We did not find any association between sex and PD survival; our data could, however, be biased because of prevalent cases.

The principal causes of death in patients with PD were heart diseases, lung infections, and cerebrovascular disease. Heart diseases and stroke were also the principal causes of death in the control group. The most striking difference from the control group was the higher frequency of deaths from pneumonia among patients with PD. As in other recent studies,31 we found no association between malignant neoplasms and PD, as previously reported elsewhere.23,33

In conclusion, despite the dramatic benefits of levodopa on the symptoms of patients with PD, its effect on survival remains uncertain. Age was the main predictor of the outcome in our patients. Pneumonia was the cause of death significantly associated with PD.

Accepted for publication October 29, 1999.

This study was supported in part by grant 58/P from the Assessorato alla Sanità della Regione Sicilia, Palermo, Italy, and by Fidia Research Laboratories, Abano Terme, Italy.

We thank the many persons at Riposto, Santa Teresa di Riva, and Terrasini who provided assistance during the study. In addition, we are particularly indebted to Walter A. Rocca, MD, MPH, Department of Health Sciences Research, Mayo Clinic, Rochester, Minn, for his helpful suggestions.

Reprints: Giovanni Savettieri, MD, Istituto di Neuropsichiatria, Università di Palermo, via Gaetano La Loggia 1, 90129 Palermo, Italy (e-mail: gsavetti@tin.it).

REFERENCES