Tuberculosis Diagnosed at Death in the United States*

Hans L. Rieder, M.D., M.P.H.;* Gloria D. Kelly, B.A.;‡
Alan B. Bloch, M.D., M.P.H.;§ George M. Cauthen, Sc.D.;; and
Dixie E. Snider, Jr., M.D., M.P.H. F.C.C.P.

From 1985 through 1988, 5.1 percent of TB cases reported in the United States were diagnosed at death. Differences in the proportions diagnosed at death by race/ethnicity, sex, and place of birth (United States vs foreign-born) were relatively small. The proportion of cases diagnosed at death increased with age, from 0.7 percent in patients less than 5 years old to 18.6 percent among patients 85 years and older. Only 26.0 percent of cases diagnosed alive were among those 65 years and older, but 60.3 percent of those diagnosed at death were in this age group. Eighteen percent of cases with miliary, meningeal and peritoneal TB were diagnosed at death, compared with 4.8 percent among those with pulmonary TB. These data indicate that TB too often remains unrecognized and that, to prevent continuing deaths from this curable disease, a high index of suspicion of TB remains important, particularly among the elderly and among persons with extrapulmonary sites of disease.

METHODS

The number of reported TB cases in the United States decreased from 84,304 in 1953 to 22,201 in 1985 and increased to 22,436 cases in 1988,1,2 As other conditions have become relatively more important causes of morbidity and mortality, a decreased awareness may result in a failure to include TB in the differential diagnosis. Failure to diagnose and adequately treat TB will lead in many cases to premature death and unrecognized transmission of Mycobacterium tuberculosis. The purpose of this analysis was to describe the characteristics of TB patients in the United States in whom the diagnosis was made at death, in order to provide clinicians with the necessary epidemiologic information required to maintain a high index of suspicion where appropriate.

MATERIALS AND METHODS

Since 1985, all states have submitted individual reports on each TB case to the CDC. The standard definition used by state and city health departments for reporting the vital status (alive or dead) to the CDC is written in the guide for completing case reports as follows: "Patients whose tuberculosis was suspected and who were started on at least two antituberculosis drugs prior to the day of death are classified as alive at the time of diagnosis even though the case is not verified and counted until after death." Before 1988, several state and city health departments did not strictly adhere to this definition.

In the years 1985 through 1987, the numbers of cases reported at death were 1,276, 1,346 and 1,402, respectively. Excluding cases misclassified as reported at death, the numbers of cases reported at death (i.e., those dying prior to the initiation of anti-TB therapy) were 1,031, 1,138 and 1,173 respectively, for the years 1985 to 1987. For 1988, there were 1,190 cases reported at death, none of which was misclassified. Thus, for the years 1985 to 1988, there were 4,541 TB cases reported at death, representing 50 percent of the four-year sum total of 89,922 reported TB cases (annual totals of 22,301, 22,768, 22,517 and 22,436, respectively). After exclusion of 3,630 cases with incomplete information on all variables of interest, 86,292 cases (96.0 percent) remained for analysis.

Status at diagnosis was categorized as a binomial outcome (alive or dead), and cases were stratified into ten age groups, five race/ethnicity groups, males or females, place of birth (United States or foreign country) and nine major disease sites. By convention, patients with both pulmonary and extrapulmonary TB are listed by the specific extrapulmonary site. Patients with more than one extrapulmonary site are classified by the major site of disease. For each variable, the stratum with the most cases was arbitrarily chosen as the reference for comparing other strata in terms of relative proportions and relative odds.

For example, the chance of delay in discovery until death in each of the disease site groups was compared with the chance among pulmonary cases because pulmonary disease was the most common site. Among the 71,199 pulmonary cases, 3,452 were not diagnosed until death, and 67,747 were diagnosed while the patients were alive. Among the 4,414 cases whose major site was lymphatic, 68 were not diagnosed until death, and 4,346 were diagnosed while the patients were alive. Thus, the observed proportion of patients with pulmonary disease diagnosed at death was 3,452/(3,452 + 67,747) = 4.8 percent and for patients with lymphatic disease diagnosed at death was 68/(68 + 4,346) = 1.5 percent; observed relative odds were (68/4,346)/(3,452/67,747) = 0.3. Adjusted relative odds of being diagnosed at death were estimated with 95 percent confidence limits by the maximum likelihood method in a log-linear categorical model, so that relative odds for patients in any particular stratum (lymphatic cases, for example) were adjusted for possible interactions.
confounding by imbalanced distribution of other patient characteristics included in the model.44

Using this model, adjusted proportions of cases diagnosed at death were estimated in strata of age, race/ethnicity, sex, place of birth and disease site. (Program written by James A. Tonascia, Ph.D., Johns Hopkins School of Hygiene and Public Health, Baltimore, MD.) Differences were considered to be statistically significantly different at p<0.05.

RESULTS

Of the 86,292 cases analyzed, 81,919 (94.9 percent) were diagnosed while patients were alive, and 4,373 cases (5.1 percent) were diagnosed at death (Table 1). Of the total cases diagnosed at death, 60.3 percent (2,636) were 65 years of age or older. The observed proportion of cases diagnosed at death increased with age from 0.7 percent in patients less than 5 years old to 18.6 percent in patients 85 years and older. Adjustments for differences in race/ethnicity, sex, place of birth and disease site indicated that the odds of being diagnosed at death for a TB patient in the oldest age group were 11.3-fold larger than for a patient in the 25- to 34-year-old reference group.

Of the total cases diagnosed at death, 48.2 percent (2,106) were non-Hispanic white, 38.1 percent were black, 9.4 percent were Hispanic, 2.7 percent were Asian/Pacific Islander and 1.6 percent were American Indian/Alaskan Native (Table 1). The observed proportions of cases diagnosed at death were lower among minorities than among non-Hispanic whites. However, after adjustment for age, sex, place of birth and disease site, the proportion among blacks was significantly higher while that among Asian/Pacific Islanders was significantly lower than the proportion among non-Hispanic whites.

Sixty-seven percent (2,930) of cases diagnosed at death were males (Table 1). The observed proportions of cases diagnosed at death were similar in males (5.2 percent) and females (4.8 percent). Adjusted propor-

Table 1—Tuberculosis Diagnosed at Death, United States, 1985-1988: No. of Total Cases, Cases Reported at Death and Alive, Observed Proportions of Cases Reported at Death, Adjusted Proportions with 95% Confidence Intervals, Adjusted Relative Odds and Probability

<table>
<thead>
<tr>
<th>Site</th>
<th>Dead</th>
<th>Alive</th>
<th>Total</th>
<th>Observed Proportions (%)</th>
<th>Adjusted Proportions (% with 95% CI)</th>
<th>Adjusted Relative Odds (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>3,452</td>
<td>67,747</td>
<td>71,199</td>
<td>4.8</td>
<td>4.7 (4.5, 4.9)</td>
<td>1*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pleural</td>
<td>214</td>
<td>3,497</td>
<td>3,711</td>
<td>5.8</td>
<td>5.5 (4.8, 6.2)</td>
<td>1.2 (1.0, 1.3)</td>
<td>0.0450</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>68</td>
<td>4,346</td>
<td>4,414</td>
<td>1.5</td>
<td>2.7 (2.2, 3.2)</td>
<td>0.6 (0.4, 0.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>59</td>
<td>1,438</td>
<td>1,497</td>
<td>3.9</td>
<td>3.6 (2.7, 4.5)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.0444</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>64</td>
<td>1,710</td>
<td>1,774</td>
<td>3.6</td>
<td>3.6 (2.7, 4.5)</td>
<td>0.7 (0.6, 1.0)</td>
<td>0.0211</td>
</tr>
<tr>
<td>Millary</td>
<td>226</td>
<td>919</td>
<td>1,145</td>
<td>19.7</td>
<td>19.0 (16.7, 21.3)</td>
<td>4.7 (4.0, 5.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Meningeal</td>
<td>110</td>
<td>603</td>
<td>713</td>
<td>15.4</td>
<td>20.4 (17.4, 23.4)</td>
<td>5.2 (4.1, 6.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>97</td>
<td>437</td>
<td>534</td>
<td>18.2</td>
<td>22.0 (18.5, 25.5)</td>
<td>5.7 (4.5, 7.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>83</td>
<td>1,222</td>
<td>1,305</td>
<td>6.4</td>
<td>6.3 (5.0, 7.6)</td>
<td>1.4 (1.1, 1.7)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*p Set = 1 for comparison.
tions were 5.3 and 4.6 percent, respectively.

Of all cases diagnosed at death, 89.9 percent (3,932) were among patients born in the United States (Table 1). By place of birth, 5.9 percent of cases among patients born in the United States were diagnosed at death, compared with 2.2 percent among foreign-born patients. Adjustment narrowed this difference to 5.4 percent compared with 4.0 percent, respectively.

Marked differences were observed in the proportion of cases diagnosed at death by site of disease (Table 1). For example, the observed proportions for pulmonary, lymphatic, and miliary TB cases diagnosed at death were 4.8, 1.5 and 19.7 percent, respectively. Of miliary, meningeal and peritoneal cases combined, 18.1 percent were diagnosed at death. Adjustment for the other variables did not appreciably change the association of disease site with the relative odds of being reported at death.

**DISCUSSION**

Over the four-year period from 1985 to 1988, 5.1 percent of nationally reported TB cases were diagnosed at death. The most important observation was that increasing age and site of disease (miliary, meningeal and peritoneal) were the variables most strongly associated with the likelihood that TB would be reported at death. That advanced age and site of disease were of overriding importance is best evidenced by the small changes in proportions of these two variables after adjustment for the other variables. By contrast, for other variables there were larger changes after adjustment. The higher crude proportions of non-Hispanic white patients diagnosed at death, compared with the proportion for patients from racial/ethnic minorities is largely explained by the much higher age of the former. In the years 1985 to 1988, the median age for non-Hispanic white TB patients was 62 years, compared with 40 years for racial/ethnic minorities. Thus, after adjustment, the proportion among blacks was actually larger than the proportion in non-Hispanic whites. The importance of TB among the elderly in nursing homes and chronic care facilities is probably substantially underestimated, as is evidenced by autopsies, and tuberculin skin test conversion rates in such facilities among health care workers and other patients.

The available information does not allow for the distinction between cases recognized at autopsy only and cases clinically suspected but with the definite diagnosis becoming available only after the patient's death. From other studies, it is known that both are relevant. Several autopsy studies have revealed that TB may be entirely missed and never suspected. Juul reported from Denmark that 0.1 percent of autopsies revealed clinically undiagnosed TB. Because only 15 percent of deaths come to autopsy in the United States, it is likely that the number of cases reported as diagnosed at death represents an underestimate. Furthermore, for those cases in whom the diagnosis is made at autopsy, the death certificate will most likely not be amended.

Late, delayed or missed diagnosis of TB has been documented as a problem as long as there has been national reporting of TB morbidity. From 1953 to 1969, the source of report for 4 to 6 percent of reported TB cases was the death certificate. From 1970 to 1988, from 4 to 6 percent of reported TB cases were reported at death. Thus, despite technological advances in diagnostic procedures, more rapid methods for the identification of *M tuberculosis*, and the availability of more effective anti-TB chemotherapy, the proportion of all TB cases with unnecessary and premature death has remained essentially unchanged.

Failure to diagnose TB may result, not only in the death of the patient, but also—in persons with pulmonary TB—may contribute to unrecognized transmission of infection to family, friends, health care workers and other contacts.

In three different studies, TB was the underlying or a contributing cause of death in up to 50 percent of TB cases unrecognized until autopsy.

Previous reports indicate that the overwhelming majority of patients reported or diagnosed at death were hospitalized prior to death, and that 50 percent of those had been hospitalized for two weeks or longer prior to death. This lengthy hospitalization of patients prior to death indicates that a "window of opportunity" exists for preventing these deaths. A recent study of TB patients with HIV infection has shown that delayed diagnosis of TB resulting in death was avoidable if adequate numbers of specimens for acid-fast smear and mycobacterial culture had been obtained and if empiric chemotherapy for TB had been administered to symptomatic patients with chest radiographs suggestive of TB.

Serious forms of extrapulmonary TB (eg, miliary and meningeal) are more often missed than other forms of TB and also more often result in death. The reasons for failing to make the diagnosis include omission of appropriate diagnostic measures for the confirmation of TB, and mistaking radiologic or clinical signs and symptoms of TB for those of malignancy, pneumonia or other conditions. Miliary TB as a cause of fever of unknown origin may be difficult to diagnose, and peritoneal TB in patients with a history of alcoholism may be mistaken as ascites solely due to cirrhosis of the liver. Similarly, the timely diagnosis of tuberculous meningitis is fraught with problems, and a high index of suspicion is warranted. In this analysis, 18.1 percent of cases of miliary, meningeal and peritoneal TB were diagnosed at death. The proportion of cases of pulmonary TB diagnosed at
death was considerably lower. However, pulmonary cases constituted 79 percent of all cases diagnosed at death. From an epidemiologic point of view, the failure to diagnose pulmonary TB is more important because of the potential for transmission of M tuberculosis. In a survey in Baltimore in the early 1960s, 44 percent of cases first registered at death were considered to have been communicable. A failure to diagnose pulmonary TB puts those who are infected by that case beyond the reach of preventive measures.

The ultimate objective of this paper is to prevent unnecessary and premature deaths from TB. Clinicians need to develop and maintain a high index of suspicion of TB disease in the elderly, in persons with uncommon forms of clinical presentation and in persons with or at risk for HIV infection. Not only must the appropriate diagnostic procedures and tests be performed, but also it is of equal or greater importance that the clinician should promptly institute effective combination antituberculosis chemotherapy based on a presumptive or empiric diagnosis of TB disease while awaiting a definitive diagnosis. A delay in the institution of therapy, particularly in meningeal or miliary disease or in pulmonary disease of undetermined etiology in persons with HIV infection, could lead to an unfortunate outcome.

This analysis demonstrates that TB too often remains unrecognized in a substantial number of patients and this leads to unnecessary and premature death. From an individual point of view, miliary, meningeal and peritoneal TB are associated with the highest risk of death. From a public health point of view, unrecognized pulmonary TB, especially among the elderly, is of greater importance, because it may lead to premature death as well as unrecognized transmission of infection in the community.

REFERENCES

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9 Edlin GP. Active tuberculosis unrecognized until necropsy. Lancet 1978; 1:850-52