Multiple Myeloma in Olmsted County, Minnesota, 1945-1964

By ROBERT A. KYLE, FRED T. NOBREGA and LEONARD T. KUIILAND

Since the causes of multiple myeloma have not been established, it would seem worthwhile to study items such as age, sex, race, long-term trends, geographic distribution, and information on occupational and familial history which might provide a basis for systematic etiologic search. Such studies, however, have been infrequent because the low incidence of myeloma has not been conducive to population surveys. In addition, the lack of electrophoretic facilities in some laboratories and the problems of diagnosis in the past, particularly before bone marrow studies became commonplace, could be expected to hamper comparisons between different populations or trend studies in the same population.

Mortality statistics for the United States indicate that the death rate for multiple myeloma per 100,000 population has doubled from 0.8 in 1949 to 1.7 in 1963. A similar trend has been reported for the United Kingdom, Scotland, and Australia; the highest rate in recent years was reported from Sweden (3.3/100,000) for 1963. Data from the Connecticut Tumor Registry show a rise in age-adjusted rates per 100,000 for males from 0.4 (1935 through 1939) to 2.5 (1960 through 1962) while the rates for females for the same period were 0.5 and 2.0, respectively.

Whether these rates reflect a true upward trend in the incidence of multiple myeloma is difficult to assess; increased availability and utilization of medical facilities and improved diagnostic methods in many areas could also account for such a trend.

To our knowledge, the only study in the United States in which an attempt was made to measure the incidence of the disease in a defined population was that of MacMahon and Clark in Brooklyn, New York, for the period 1943 through 1952. They noted an average annual incidence of 1 and 1.3 per 100,000 for the white and Negro populations, respectively.

In this report a unique source of medical information built around the record system of the Mayo Clinic has been utilized in an attempt to define the trend and demographic characteristics of multiple myeloma cases since
1945 in the predominantly white population of Olmsted County, Minnesota. The paucity of information available before 1945 precluded a detailed analysis for any earlier years.

**BACKGROUND**

The medical practice in Rochester and surrounding Olmsted County, Minnesota, has centered largely at the Mayo Clinic. Records of the Mayo Clinic and other institutions in the community lend themselves to various studies, particularly for diseases of a serious progressive nature such as multiple myeloma. The medical indexing and record-retrieval system that has been developed over the past several decades at the Mayo Clinic and other institutions in Rochester ensures the identification of practically all persons from the city and the surrounding county in whom a serious illness was diagnosed. Diagnoses made by physicians at the Mayo Clinic, at affiliated hospitals, on home visits, or at autopsy are entered on the master sheet of the patient's clinic record, indexed, and processed for automated retrieval. Diagnoses on the medical records of residents hospitalized in other institutions in Rochester and surrounding counties have been coded and indexed by diagnosis; the availability of such data ensures reasonably complete ascertainment of major illnesses in the population of the county.\(^5,6\)

The population of Olmsted County has increased from 43,000 in 1940, to 48,000 in 1950, to 65,000 in 1960.\(^7\) At present, approximately 60 per cent of the residents of the county live within the city of Rochester; this 60:40 urban-rural ratio has remained relatively constant over the past 30 years. Since the primary occupation of those living outside of Rochester is agricultural and none of the surrounding 13 villages has more than 2,000 inhabitants, the residents of Rochester were classified as urban, while those in the remainder of the county were considered rural.

**MATERIAL AND METHODS**

For county residents, all diagnoses such as myeloma, multiple myeloma, plasmacytoma, extramedullary plasmacytoma, plasma cell dyscrasia, dysproteinemia, Bence Jones proteinuria, and hyperglobulinemia were obtained from the records of the Mayo Clinic and its affiliated hospitals, the Olmsted Community Hospital, the Rochester State (Mental) Hospital, all hospitals in the adjacent counties, and the University of Minnesota Hospitals and the Veterans Administration Hospital in Minneapolis.

Patients were considered to have multiple myeloma if their bone marrow showed increased numbers of abnormal plasma cells and if at least one of the following three features was present: 1) paraprotein in serum electrophoresis, 2) paraprotein in urine electrophoresis or Bence Jones proteinuria, or 3) lytic bone lesions or pathologic fractures; or if autopsy findings were typical of multiple myeloma, or if histologically proved solitary myeloma were present. All patients had clinical features consistent with myeloma.

In addition, all death certificates of Olmsted County residents reporting the aforementioned diagnoses during the period 1935 through 1964 were reviewed. Furthermore, an effort was made to obtain the clinical records, peripheral blood smears, bone marrow slides, and autopsy protocols for all cases. Only those patients who had lived in Olmsted County prior to the onset of symptoms were considered to be bona fide residents. Any person known to have moved to Olmsted County merely to facilitate the diagnosis and treatment of an existing disease was excluded.
MULTIPLE MYELOMA

Table 1.—Number and Average Annual Incidence Rate/100,000 for Each Decade for Cases of Multiple Myeloma Among Residents of Olmsted County, Minnesota, 1945 Through 1964

<table>
<thead>
<tr>
<th></th>
<th>1945 through 1954</th>
<th>1955 through 1964</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Population</td>
</tr>
<tr>
<td>Males</td>
<td>8</td>
<td>22,697</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
<td>25,531</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>48,228</td>
</tr>
<tr>
<td>Adjusted rate*</td>
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* Adjusted to the 1950 U.S. white population.

RESULTS

Myeloma was diagnosed in 35 Olmsted County residents over a 20 year period, from 1945 through 1964. The initial diagnosis of 31 of these patients had been made at the Mayo Clinic. Two cases were reported at the Olmsted Community Hospital and one case each at the Rochester State Hospital and the Zumbrota Community Hospital. Bone marrow slides were available for review in 27 cases, postmortem examination in 17, and tissue from vertebral biopsy specimens in 3. In two cases tissue was not available for review but each of the two patients had had lytic bone lesions, monoclonal peak in the serum or Bence Jones proteinuria, and a clinical picture which was consistent with myeloma.

One of the 35 patients had had a solitary plasmacytoma and remained well for 7 years when he died suddenly of coronary artery disease. Autopsy was not performed.

Of the 35 patients, 22 were males and 13 were females. The average annual incidence rate for the total population was 3.1/100,000 in each decade (1945 through 1954 and 1955 through 1964). When age adjusted to the 1950 U.S. white population, the rates were virtually identical to the crude rate, being 2.9 and 3.0/100,000 respectively (Table 1). The overall incidence rate for the 20-year period for males was 4.1/100,000 while that for females was 2.2/100,000. The standard errors of these rates are 0.9 for males and 0.6 for females. The male: female ratio was 1.9:1, a distribution which was in accord with the figures reported by McFarlane* and Martin.9 According to most reports, the incidence is nil before the age of 30 years, increases to a maximum in the age group of 50 to 70 years, and then decreases.9,10 In the Brooklyn, New York, study,4 the age-specific incidence rates for the years 1943 to 1952 showed a gradual increase to about age 65 and then declined. Although the numbers are small in Olmsted County, the average annual incidence rate increased with age and was highest for males 80 years of age and older and for females 70–79 years of age (Table 2). The sex ratio has been reported as 1:1 for those under 65 years of age with a predilection for males over this age. In Olmsted County the male:female ratio is about 1:1 up to age 60 years, after which it is about 2:1 (males to females).

In Olmsted County, the incidence of myeloma was only slightly higher in males who lived in rural areas than among those in urban populations, while
Table 2.—Number and Incidence Rate/100,000 by Age and Sex of Patients With Multiple Myeloma Among Residents of Olmsted County, Minnesota, 1945 Through 1964

<table>
<thead>
<tr>
<th>Age, yr.</th>
<th>Male No.</th>
<th>Rate</th>
<th>Female No.</th>
<th>Rate</th>
<th>Total No.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>1</td>
<td>1.3</td>
<td></td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>1</td>
<td>1.6</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>50–59</td>
<td>1</td>
<td>2.0</td>
<td>2</td>
<td>3.5</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>60–69</td>
<td>7</td>
<td>18.6</td>
<td>2</td>
<td>4.6</td>
<td>9</td>
<td>11.1</td>
</tr>
<tr>
<td>70–79</td>
<td>7</td>
<td>33.9</td>
<td>6</td>
<td>22.4</td>
<td>13</td>
<td>27.4</td>
</tr>
<tr>
<td>80+</td>
<td>5</td>
<td>68.7</td>
<td>2</td>
<td>17.4</td>
<td>7</td>
<td>37.4</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>4.1</td>
<td>13</td>
<td>2.2</td>
<td>35</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Adjusted rate* 3.1

* Adjusted to the average 1950 and 1960 U.S. white population.

Table 3.—Number and Incidence Rate/100,000 by Sex and Residence Among Multiple Myeloma Cases in Olmsted County Residents, 1945 Through 1964

<table>
<thead>
<tr>
<th></th>
<th>Males No.</th>
<th>Rate</th>
<th>Females No.</th>
<th>Rate</th>
<th>Total No.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>10</td>
<td>4.5</td>
<td>3</td>
<td>1.4</td>
<td>13</td>
<td>3.0</td>
</tr>
<tr>
<td>Urban</td>
<td>12</td>
<td>3.8</td>
<td>10</td>
<td>2.5</td>
<td>22</td>
<td>3.1</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>4.1</td>
<td>13</td>
<td>2.3</td>
<td>35</td>
<td>3.1</td>
</tr>
</tbody>
</table>

for females the opposite was true. The differences, however, were insignificant and for both sexes combined the incidence rate for urban and rural residents was virtually identical (Table 3).

Thirty-one of the 35 patients with myeloma have died. Sixteen of the 31 (52 per cent) died within a year after onset of symptoms while an additional 6 (total of 22 or 71 per cent) died within the first 2 years after onset. Eight of the remaining nine patients died within 8 years, while the ninth died 18 years after onset. This last patient was found initially to have a solitary myeloma which ultimately disseminated. The mean survival for the 35 patients was somewhat more than 2 years and the median survival was only slightly more than 1 year.

Death certificates were obtained for the 31 patients. Multiple myeloma was reported as the underlying cause of death in 23 (74 per cent) of these. Death in two of the remaining eight cases was attributed to cardiovascular disease, in two cases to cerebrovascular disease, and in one case each to pancytopenia, tuberculosis, chronic renal disease, and carcinoma of the cheek. Since about one of four cases of myeloma would have been missed by reviewing the death certificate alone, it would appear that if one can generalize from this experience, studies limited to death certificates would provide underestimates of the true incidence of multiple myeloma. Of further interest is the fact that all local residents identified on the death certificates as having multiple myeloma had already been identified through one of the clinical sources of information.
COMMENT

Published official death rates for multiple myeloma were not available until the 1948 revision of the International Classification of Diseases. Since that time the reported crude death rate for multiple myeloma in the United States has risen from 0.8/100,000 to 1.7/100,000 in 1963. A similar increase was reported for many European and other countries having such statistics. In Olmsted County, Minnesota, the average annual incidence rates for myeloma increased from nearly 1/100,000 in the early decade (1935 through 1944) to approximately 3/100,000 in the past two decades. The low rate for the first decade is probably best explained by the infrequency of bone-marrow examination and the inadequacy of serum and urinary protein studies as well as a lesser clinical appreciation of myeloma during that period. Since 1945 the rates in Olmsted County have been similar to those in at least two other studies reported from other areas. In Malmo, Sweden (population 200,000), from 1950 through 1959, Waldenström reported 61 cases of multiple myeloma. If all these patients were local residents, the average annual incidence of myelomas would be 3/100,000; in the Registrar General’s report for England (1958), the incidence rate for myeloma was calculated to be 2.6/100,000.

In the Brooklyn study referred to earlier, MacMahon and Clark reported average incidence rates of 1 and 1.3 per 100,000 for the white and Negro populations, respectively. They emphasized at the time that the rate of myeloma among Negroes, when standardized to the age distribution of the white population, was 2 1/2 times that of the white race or 2.5/100,000. This rate among Brooklyn Negroes from 1943 through 1952 is only slightly less than that found for the white population of Olmsted County from 1945 through 1954. Assuming there is no geographic variation per se, these findings suggest a lower degree of case ascertainment in the white population of Brooklyn than in Olmsted County.

In Jamaica, McFarlane noted that between 1962 and 1964, 40 patients (all but one were Negro) with myelomatosis were observed at the University of the West Indies. It was the author’s impression that the university’s laboratory served 400,000 persons and therefore he estimated that the average annual incidence rate was about 5/100,000. However, the uncertainty of the time of occurrence in his cases and the true population at risk raise some question as to the accuracy of this estimate.

Another study indicative of racial or national differences was reported from Israel. It revealed a slightly higher rate among American or European-born Jews as compared to those of Asian-African origin. In that study the annual incidence per 100,000 population for persons 30 years of age and older was 4.7 for the immigrants from American and Europe and 3.6 for those from Asia and Africa.

When the rates for Olmsted County are computed in the same way, that is, for those 30 years of age and older, the rate is 6.3/100,000. The standard error for this rate is 1.1/100,000. The higher rate in Rochester probably reflects more complete case ascertainment.

Most clinical series have reported a peak frequency of myeloma among
persons between 50 and 60 years of age. Even in the Brooklyn study, the peak incidence appeared among patients approximately 65 years of age with a decline among persons more than 70 years of age. In Waldenström’s study in Malmo, the greatest incidence was among persons in the eighth decade of life; however, no age-specific rates were reported. In Olmsted County, where the medical resources which were surveyed included the general as well as the specialist practice for the community, the incidence rate for a 20 year period increased with age with the highest rate in males 80 years of age and over and in females 70 years of age and over; this finding suggests that the pathogenic mechanism of myeloma may not be different from that of most other malignancies in adults. It also suggests that in hospital series and in some population studies dependent on limited sources of medical information, the proportion of older affected persons may be underestimated since younger patients are selectively admitted to most diagnostic centers.

**Summary**

All cases of multiple myeloma diagnosed in bona fide residents of Olmsted County, Minnesota, during the years 1945 through 1964 were identified and reviewed. Pathologic material was available for reconfirmation of the diagnosis in 33 of the 35 cases reported. In the remaining two cases the diagnosis was based on roentgenologic findings and protein abnormalities as well as a typical clinical picture. The incidence rate for males was 1.9 times that for females. During the 20 year period covered in this study the average annual incidence rate in the total population has remained about 3/100,000 and when computed for persons 30 years of age and over, it is 6.3/100,000. Incidence figures by place of residence did not reveal a significant difference in the urban-rural rates. Myeloma was listed as a cause of death in 74 per cent of the death certificates. The mean survival time from onset in all cases was about 2 years, with a median survival of approximately 1 year. The age-specific rate increased with age, the highest rates being among male residents 80 years of age and older.

**SUMMARIO IN INTERLINGUA**

Omne le casos de myeloma multiplice diagnosticate in subjectos documentatemente residente in le contato de Olmstead (Minnesota) durante le annos ab 1945 ad (e incluse) 1964 esseva identificate e revistate. Materiales pathologic esseva disponibile pro reconfirmar le diagnose in 33 del 35 casos reportate. In le remanente duo casos, le diagnose esseva basate super constatationes roentgenologic e anormalitates proteinic insimul con un typic tableau clinic. Le incidentia in masculos esseva 1,9 vices illo in femininas. Durante le periodo de 20 annos considerate in iste studio, le valor medie del incidentia annual in le population total esseva aproximativemente 3 pro 100.000. Recalculate pro subjectos de 30 annos de etate e plus, le valor es 6.3 pro 100.000. Le datos de incidentia differentiate secundo le locos de domicilio non revelava significative differentias inter areas urban e rural. Myeloma esseva notate come causa de morte in 74 pro cento del 35 certificatos de morte. Le duration medie del superviventia post le declaration del morbo esseva pro le grupp total aproximativemente 2 annos. Le superviventia median esseva aproximativamente 1 anno. Le incidentia differentiate secundo le grupp de etate revelava un crescente incidentia con le aumento del etate. Le valor le plus alte esseva constatate inter residentes mascule de etate de 80 annos e plus.
ACKNOWLEDGMENT

Autopsy tissue was reviewed by Dr. Edgar C. Harrison, Jr.

REFERENCES

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