Volume 1

Neoplastic Diseases of the Blood

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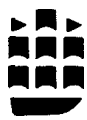

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Etiology and Epidemiology of Multiple Myeloma and Related Disorders

Linda M. Pottern, M.P.H.
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The first case of "mollities ossium" was documented over 135 years ago in a 45-year-old English tradesman. A series of classic reports of this case summarized a number of important clinical, pathologic, and laboratory features of the disease. Particularly relevant was the discovery of Bence Jones protein in the urine which established that multiple myeloma was a disease characterized by abnormalities of protein metabolism.[21]

Multiple myeloma is the prototype of a group of conditions known as monoclonal gammopathies. A common presenting complaint is bone pain or pathologic fracture associated with radiographic evidence of "punched-out" bony destruction. This clinical characteristic has resulted in myeloma being traditionally classified as a bone tumor for purposes of disease classification. However, since 1950 myeloma has been assigned code number 203 under the category of "neoplasms of lymphatic and hematopoietic tissues" in the sixth, seventh, eighth, and ninth editions of the ***Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.***[140]

Benign monoclonal gammopathy (BMG) or monoclonal gammopathy of undetermined significance (MGUS) (Chapter 33) is a laboratory diagnosis when an M-spike is discovered coincidentally on routine medical examination. The benign designation is made when other clinical stigmata of myeloma are absent and the M-spike remains quantitatively static over time.[66] Waldenstrom's macroglobulinemia (WM) is a rare lymphomatous malignancy of cells that appear to bridge the gap between lymphocytes and plasma cells.[136] These so-called lymphocytoid plasma cells secrete IgM, and many of the bizarre clinical manifestations of this disease arise because of the unusual physiochemical properties of this "macroglobulin."[67] In recent years, with improvements in the diagnosis and reporting of myeloma and related disorders, interesting patterns of disease occurrence have been recognized which suggest opportunities for etiologic study.

Demographic Features

According to the most recent United States incidence data, 1973 to 1977, from the Surveil-

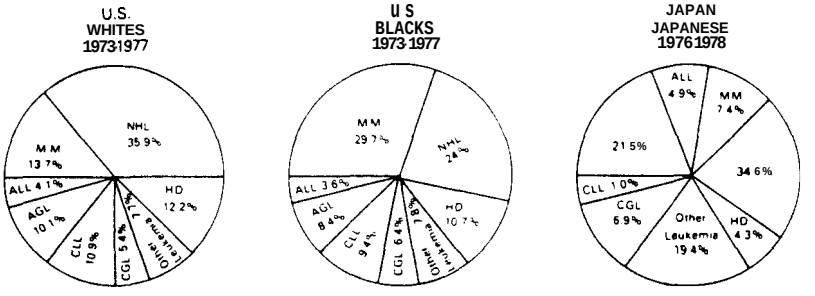


Fig. 22–1 Relative proportion of lymphoreticular malignancies in U.S. whites and blacks[144] and Japanese in Japan.[122] **AGL,** acute granulocytic leukemia, **ALL,** acute lymphoblastic leukemia: **CGL,** chronic granulocytic leukemia; **CLL,** chronic lymphocytic leukemia; HD, Hodgkin's disease; **MM,** multiple myeloma: **NHL,** non-Hodgkin's lymphoma.

lance, Epidemiology, and End Results (SEER) Program, multiple myeloma accounts for 1.1 percent of all malignancies in whites and **2.1** percent in blacks.[144] The average annual age-adjusted **(1970** U.S. standard) incidence rates for whites are **4.3** per **100,000** in males and **3.0** in females, while for blacks, the rates are **9.6** in males and **6.7** in females.[144] Figure **22–1** illustrates that multiple myeloma is the **most** common form of malignancy of the lymphohematopoietic system in blacks **(29.7** percent) while it is the second most common in whites **(13.7** percent). Non-Hodgkin's lymphomas account for 24.0 percent in blacks and **35.9** percent in whites.

A distinctive feature of myeloma is its late age of onset. The median age at diagnosis is 68.4 for males and 69.8 for females. The average annual age-specific incidence curves for the United States, 1973 to 1977, are shown by race and sex in Figure 22–2.[144] The rates increase with increasing age for both sexes and races. Blacks have higher rates of myeloma than whites at all ages except for the oldest age group, 85+. **A** male predominance is seen in both races, although black females have higher rates than white males.

The age patterns of mortality for multiple myeloma closely parallel the incidence curves. The median age at death is 69.6 years for males and **71.3** years for females.[12] Shown in Figure **22–3** are the age-specific mortality rates for multiple myeloma in the United States from 1950 to 1975.[12] These patterns demonstrate that multiple myeloma affects primarily persons beyond 55 years of age. Nonwhite rates exceed white rates in all age groups, and peak

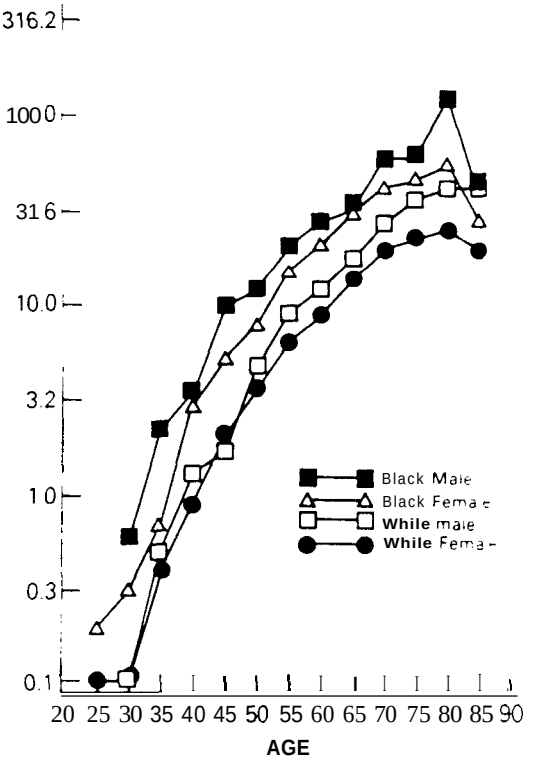
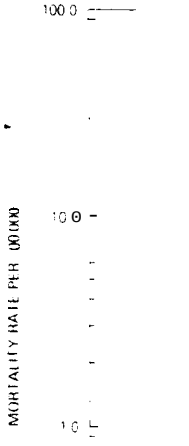
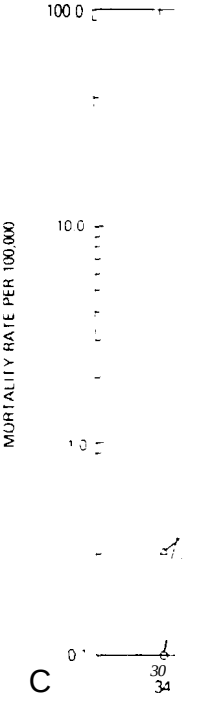


Fig 22-2 Multiple myeloma, age-specific incidence for United States, 1973 to 1977[144] Rates per 100,000





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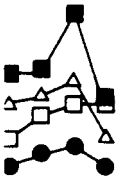

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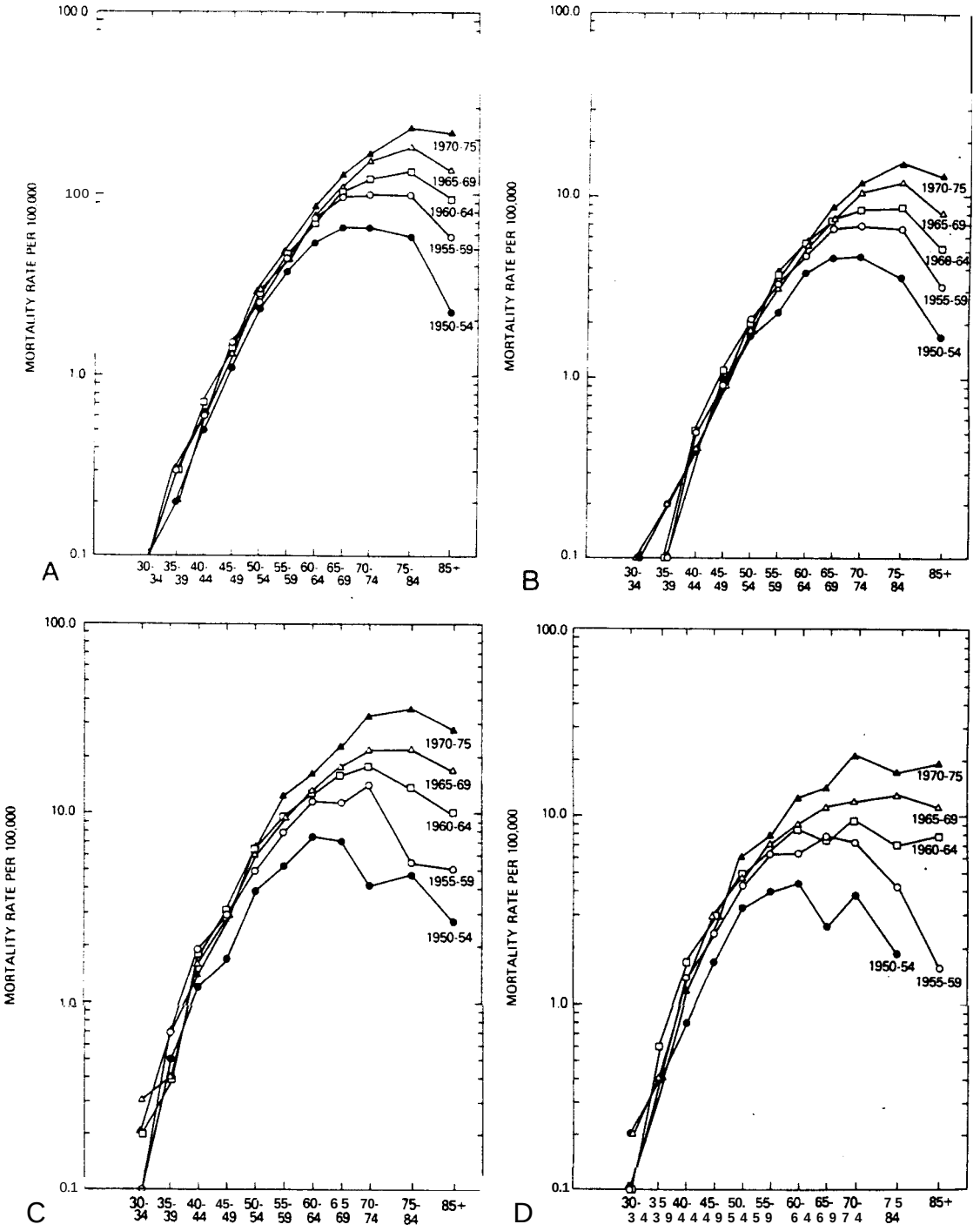


Fig. 22–3. Multiple myeloma, age-specific mortality for United States, 1950–1975. Rates per 100,000.[12] (A) Top left, white males; (B) top right, white females; (C) bottom left, nonwhite males; (D) bottom right, nonwhite females. (Blattner WA, Blair A, Mason TJ: Multiple myeloma in the United States, 1950–1975. Cancer 48:2547, 1981.)

mortality occurs for both between ages 70 and 80.

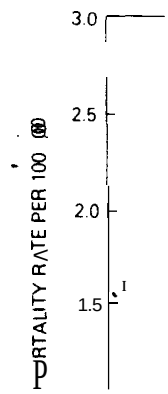
The incidence of multiple myeloma in the United States appears to be increasing. However, it is questionable to what extent this increase is due to improved case ascertainment or diagnostic practice. A comparison between the incidence data from the Second National Cancer Survey, 1947 and the Third National Cancer Survey (TNCS), 1969 to 1971 shows that the percentage increase in reported rates for myeloma was greater than for any other form of cancer.[40] The upward trend was greater among blacks than whites, especially at older ages. Comparison of the TNCS age-adjusted incidence rates[23] to more recent 1973 to 1977 calculations[144] from the SEER program reveals an 18.5 percent increase in the rates of myeloma in black males and appreciably smaller percent increases in black females, white males, and white females (3.1 percent, 7.5 percent, and 11.1 percent, respectively). This suggests that improved case ascertainment or altered diagnostic practices, which were unlikely to have occurred between these two recent time periods, may be responsible for only part of this increase in incidence.

During the 25-year period, 1950 to 1975, there has been an increase in myeloma mortality paralleling the rise in multiple myeloma incidence. The bulk of the increase for each race–sex category is seen in the 60-year and older age groups (Fig. 22–3).[12] This rise in the rate in older age groups over the past 25 years may reflect improvement in death certification.[99] Mortality rates have increased over each time period, with nonwhite males having the highest increase. The proportionate increase in mortality during this 25-year period for nonwhites was 207 percent for males and 210 percent for females, while for whites the increase was not as great, 108 percent for males and 89 percent for females. The rise in multiple myeloma mortality from 1950 to 1975 has been relatively linear for both races and has occurred in all geographic regions of the United States (Fig. 22–4).[12] Although the nonwhite rates show some fluctuation due to relatively small numbers in certain regions, the rise in mortality has been more pronounced than among whites. During this time period the male fraction of cases has remained relatively constant at approximately 58 to 60 percent for both races. The contribution of blacks to the total myeloma burden has increased from 54 to 65 percent.[12]

Time trends in incidence from selected population-based registries from around the world are shown in Figure 22–5.[130,131] For some registries, slight increases in incidence are observed for the two most recent time periods, while in the majority no significant change over time is seen.

A number of studies have attempted to define the source of this rising myeloma incidence and mortality. Linos and colleagues[73] reviewed the time trends in incidence of myeloma in Olmsted County, Minnesota, for the past 33 years. The average annual incidence rates for multiple myeloma in Olmsted County between 1945 and 1977 were 2.9, 3.0, and 2.7 per 100,000 for each of the three decades of the survey. These data suggest that the apparent increases in myeloma reflect the underdiagnosis of this entity in the past rather than a true increased incidence.[73] However, Olmsted County has a relatively homogeneous population with regard to race, ethnic background, and occupation, with blacks comprising a negligible proportion of the population. Yet, in the United States, the most marked changes in the incidence of myeloma are occurring among blacks.

Valez et al.[127] examined the national death statistics for England and Wales for the period 1950 to 1979 to determine whether the secular trends in myeloma mortality are due to biases associated with improvements in medical care. Age-adjusted mortality increased more than fivefold during the 30-year time period of the study, with the greatest apparent increase occurring in individuals over 70 years of age. Analysis of mortality by social class and region points toward improved case ascertainment as being responsible for at least part of the apparent increase. The rise in mortality



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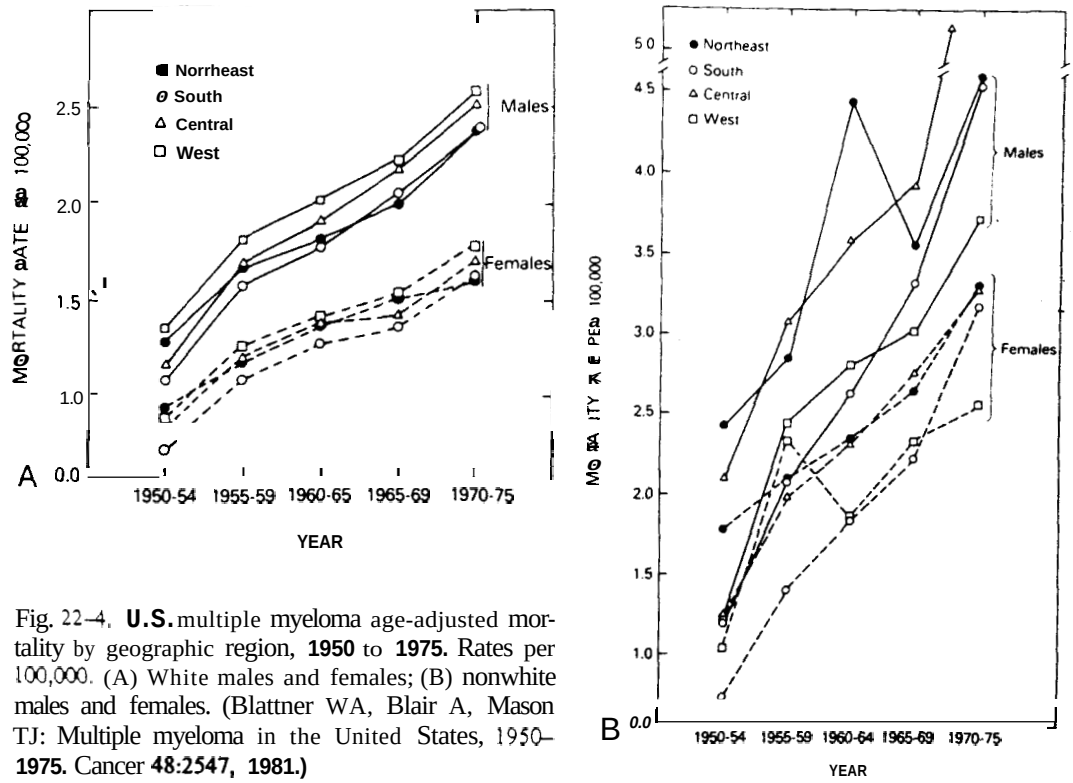

Fig. 22–4. **U.S.** multiple myeloma age-adjusted mortality by geographic region, **1950** to **1975.** Rates per 100,000. (A) White males and females; (B) nonwhite males and females. (Blattner WA, Blair A, Mason TJ: Multiple myeloma in the United States, 1950–**1975.** Cancer **48:2547, 1981.)**

at younger ages could, however, reflect a true increase. Ludwig et **al.**[74] also reported an increasing trend in mortality for multiple myeloma between 1969 and 1979 in Austria, but the reason for this increase is unknown. Since most studies document the largest increases in the oldest age groups, it is likely that the majority of the increase represents improvements in medical diagnosis and death **certification.**[99] However, the rise in younger age groups could be a harbinger of emerging increases associated with more recently introduced etiologically linked environmental exposures (see below).

Socioeconomic status may be associated with mortality from multiple myeloma. Based on data from the Registrar General for England and Wales, a socioeconomic gradient in multiple myeloma mortality appears to exist, with the highest rates in the upper social **class.**[105-107] Analysis of U.S. mortality data at the county level for 1950 to 1969 also indicates a positive association with higher socioeconomic status, which may be a reflection of patterns in diagnostic practice and **ascertainment.**[48] This explanation is consistent with the diminution of the social class effect over time in Great Britain, associated with wider dissemination of uniform health care to all classes. However, using incidence data from the **TNCS,** including census tract information on social class, **DeVesa**[30] found **a weak** inverse association between income level and myeloma incidence. The rates among blacks remained higher than whites after adjustments were made for differences in income.

The prognosis for multiple myeloma is poor. The 5-year survival rate for 1973 to 1979 provided by the SEER program is 22 percent for whites and 23 percent for blacks [Ries L: personal communication (unpublished data)]. These are population-based figures (covering 10 percent of U.S. population), whereas earlier statistics showing more favorable survival for blacks than whites used primarily hospital-based **data.**[6]

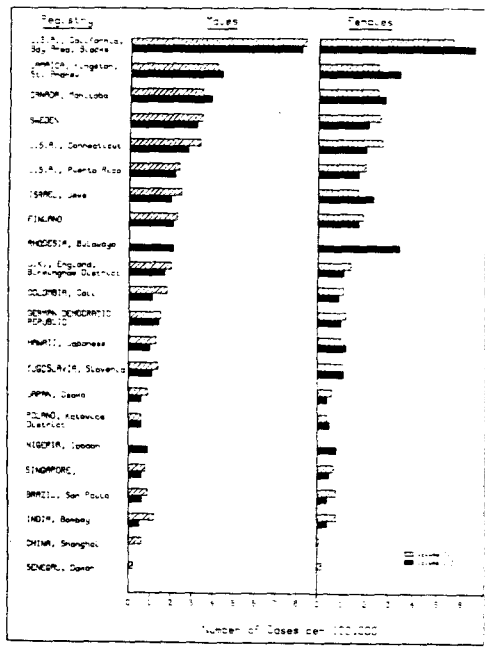

Fig. *22–5.* Multiple myeloma, age-adjusted incidence (world standard population) **from selected** registries. Rates **per 100,000.**[130,131]

Data from a recent comparative hospital-based record review conducted by Savage et **al.**[113] revealed poor survival rates in blacks with **myeloma.** Several indexes of poverty best explained the lower survival pattern. Even when ***cases*** were matched for clinical stage and race, the indexes of poverty were the best correlates of poor survival.

The epidemiologic patterns of **BMG** and WM[11] resemble those for myeloma. Both **BMG** and **WM** share a strong old-age dependence. However, accurate incidence data are not available since neither **is** classified as a malignancy by standard hospital coding practice. However, **for** WM the rate in hospital-based surveys is approximately one quarter that of multiple myeloma.[11]

Racial and Geographic Variation

Comparisons between international incidence rates of myeloma based on cancer registry data must be made cautiously since the populations served vary in size and age distribution, in the accuracy of case ascertainment (e.g., pathology vs death certificate only), and in the level of medical care and diagnostic precision.[130,131] According to the most recent editions of ***Cancer incidence in Five Continents,*** black rates in several U.S. registries were among the top for both males and females.[131]

The excess among blacks in the United States was described by MacMahon and Clark[76] and confirmed by McPhedran et al.,[86] who reported that myeloma was twice as common among blacks in Atlanta, Georgia. The rates also appear to be high in Jamaica, where blacks have a relatively young median age at diagnosis (50 to 55 years) and a **low** average survival due to the advanced stage at presentation.[123]

While high rates occur in American black populations, blacks in Africa generally have low rates (Fig. 22–5).[130,131] The difference may be explained by the small percentage of older blacks, limited diagnostic facilities, and incomplete ascertainment. However, in a recent survey of myeloma cases seen between 1973 and 1975 at hematology clinics in Johannesburg, South Africa, the age-adjusted (world standard) rates for black males (7.47/100,000) and females (5.11/100,000) closely resembled the incidence rates reported in U.S. blacks for a comparable period.[13] Case series from French West Africa,[97] Rhodesia,[129] Zambia,[126] Nigeria,[53] Kenya,[96] and South Africa[31] suggest a younger median age at diagnosis and a sizable male excess (in some series by as much as 4 to 1).

In Nigeria[34,35] and Uganda,[139] a striking proportion of the myeloma cases have been reported in young people. Since Burkitt's lymphoma is endemic in these areas, there may be common etiologic factors (e.g., malarial infestation) for these B-cell tumors.

In Latin America, the incidence data for multiple myeloma are lacking, mainly as a result of underdiagnosis and incomplete reporting. An interesting observation comes from El Salvador, where a peculiar form of

plasmacytoma has been reported to complicate long-standing rhinoscleroma. In these patients, chronic nasal infection with ***Klebsiella rhinoscleromatis*** predisposes to local plasmacytic infiltration with potential for malignant transformation as plasma cell leukemia.[5]

Among Western countries, the rates in Scandinavia are similar to those in the North American white population, while the rates are slightly lower in England and substantially lower in Eastern European countries (Fig. 22–5). In Norway, Stalsberg[121] reported that multiple myeloma is the most frequent form of Lymphoreticular malignancy (32 percent), with higher rates in the rural population over 60 years, a finding that parallels that of Kyle et al.[68] in the United States. High rates were also suggested for Ireland[36] and Scotland,[27,104] although based on small numbers of cases.

Ludwig et al.[74] report a relatively low incidence of multiple myeloma in Austria and comment that the apparent north–south gradient in Europe could reflect ethnic differences, although quality of reporting is a contributing factor. This conclusion is supported by an analysis of U.S. mortality data which also shows a north–south gradient and a statistically significant ethnic association with persons of Scandinavian ancestry.[12]

The incidence of myeloma is low in several Asian countries, including the People's Republic of China,[89] South Korea,[64] and Japan.[10,122,132] Rates in U.S. Oriental populations closely resemble those of their native countries.[132] A comparison of age-specific mortality rates for Japan (1969 to 1973) to white and nonwhite rates in the United States for a comparable period (1970 to 1975) confirms that multiple myeloma is less common in Japan, with the differences most marked in older age groups.[11]

As shown in Figure 22–1 comparing U.S. whites and blacks to Japanese in Japan for various lymphoreticular neoplasms, there is a relative deficit of malignancies of mature lymphoid cells in Japan.[122] While the total percent of all cancers attributed to non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia (CLL) is 60.5 percent for U.S. whites and 63.1 percent for U.S. blacks, the percentage in Japan is 43 percent. This shift results almost entirely from the extreme deficit of CLL in Orientals[132] and a low occurrence of multiple myeloma. This low rate of differentiated B-cell malignancies probably reflects genetic factors[132] as well as the excess of T-cell malignancies in Japan,[122] which appears to be related to the newly recognized human T-cell leukemia virus (HTLV).[61,109,110] A role for genetic factors is also suggested by the higher percentage of immunoglobulin D (IgD) myeloma in Orientals.[72,95] Since IgD involves a less-differentiated plasma cell, this increase may be consistent with the tendency of Orientals to develop undifferentiated, as opposed to differentiated, forms of B-cell neoplasms.[11]

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Environmental determinants of multiple myeloma have not been well documented in the epidemiologic literature. Case-control studies of myeloma patients have only recently been undertaken in several centers and the findings have not yet been reported. The scarcity of studies is primarily due to the inherent methodologic problems associated with investigating a rare disease of older individuals who have a poor prognosis. The majority of the etiologic information has been provided by county mortality data, cancer surveys, mortality studies of specific occupational groups, and clinical case reports."

Several large studies that have reported associations between specific occupations or industries and multiple myeloma are presented in Table 22–1.[1,2,12,88,135] These data must be interpreted with caution since some of the associations may have occurred by chance alone as a consequence of multiple comparisons.

Farming has been suggested as a possible risk factor for myeloma although the evidence is weak. Bross et al.[17] reported a nonsignificant excess of dairy farmers among patients who developed myeloma. In Texas, mortality rates

Table 22–1. Reported Associations Between Industry or Occupation and Multiple Myeloma: General Studies

Study	Year	Industry or Occupation	Study Design
Blattner et al.[12]	1981	U.S. county mortality data, 1950–1969 Petroleum manufacturing (WM)* Paper manufacturing (WM)† Furniture manufacturing (WM)‡	Correlated age-adjusted mortality rates in state economic areas with selected manufacturing industnes
Agu et al.[2]	1980	State of Texas, 1969–1971 Agriculture; Beauty shops* Carpentry* Mining'	Correlated age-adjusted mortality rates in Texas state economic areas with selected occupations, controlled for percentage of blacks in population, problem data not presented separately for males and females
Milham[88]	1976	Washington State, 1950–1971 Foresters and conservationistsf Paper and pulp mill workers* Plywood workers‡ Construction and building contractors$ Plasterers and latherers‡	Proportionate mortality analysis of death certificate occupational statement and cause of death for men aged 20 and older
Adelstein[1]	1972	British census, 1961 Administrators/managers* Professional/technical workers and artists† Painters and decorators‡ Food, drink, and tobacco workers‡	Proportionate mortality analysis of census occupational data and cause of death for males aged 15–74; problems: (1) denominator includes only 10% sample of census, (2) length of employment not designated
Williams et al.[135]	1977	Third National Cancer Survey, 1969–1971 Sales personnel (M, F)* Manufacturing (M, F)$	Interview data on main lifetime occupation, and so forth, from a 10% sample of individuals identified in the Survey; problems: (1) poor response rate (57%), (2) based on relatively small numbers in many occupational groups

Abbreviations: F, female; M, male; WM. white male.
* $P < 0.05$.
† $P < 0.01$.
‡ Not statistically significant.

of myeloma have been positively correlated with areas that employ a high percentage of the population in agricultural industries.[2] This is in contrast to the total United States, where significantly lower rates have been noted among rural residents living on farms."' A death certificate analysis of 261 myeloma cases and matched controls conducted in Washington State revealed a significant association between farming occupations and death from myeloma.[88] Similar studies using Nebraska[15] and Wisconsin[Z0] death certificates also showed an association with farming. In the Nebraska study, decedents who had resided in counties with high levels of pesticide use had elevated, but nonsignificant risks of multiple myeloma, while significant excesses were noted among residents of Wisconsin counties with high insecticide use. Similar findings were also reported for non-Hodgkin's lymphoma in Wisconsin, suggesting shared etiologic relationships for these types of B-cell malignancy.[n] Due to possible misclassifications of occupation and cause of death on death certificates, such results should be viewed with caution.

Exposure to metals has been reported as a potential risk factor. Greene et al. found a relative excess of myeloma deaths in male employees of the Government Printing Office. Cases were confined to compositors, whose major exposure was to molten lead and lead vapor.[44] The presence of trace levels of lead and cadmium in U.S. water supplies has also

been positively correlated with mortality from multiple myeloma.[7]

Males residing in U.S. counties that manufacture synthetic rubber and synthetic fibers appear to have elevated rates of myeloma.[80] The findings of an increased risk of myeloma in the rubber industry have been inconsistent.

One mortality study of rubber workers found an excess of myeloma among female workers although no specific job was associated with the risk.[91] White male employees were not at increased risk.[90] A similar study of female production workers in a rubber manufacturing plant also revealed no excess deaths from myeloma.3

Employment in wood-related industries such as paper and furniture manufacturing, paper, pulp, plywood and lumber, and carpentry has been associated with excess deaths from myeloma (Table 22–1). Petroleum refinery and petrochemical workers,[16,28,125] cosmetologists and beauty shop employees,[2,45] and leather workers[29,33] may also be at increased risk of myeloma. Decoufle et al.[28] noted that the benzene exposure in their petrochemical plant cohort may have played an etiologic role in the pathogenesis of several tumors of B-cell lineage since two cases of myeloma and a case of CLL were observed. A benzene link was also suggested by a case report from Japan by Nakayama et al.[93] of a conjugal cluster where both husband and wife experienced 30 years of exposure to benzene hexachloride related to agricultural employment. Several case reports have linked asbestos exposure to lymphoproliferative neoplasms, including myeloma,[42,56-58,71] but this association has not been seen in the follow-up studies of asbestos workers.[116]

The role of drugs has been suggested by case reports of myeloma following use of phenytoin (Dilantin)[83] and sulphinpyrazone.[138]

Radiation Exposures

Exposure to ionizing radiation is the best documented risk factor of multiple myeloma but the mechanism by which the radiation induces the cancer has not yet been established.[10,24] The strongest evidence linking radiation to myeloma has been provided by a recent report on the mortality experience of 109,000 atomic bomb survivors. Twenty-nine multiple myeloma deaths were identified over the years 1950 to 1976.22 of which were exposed to the bomb. Those survivors who received 50 or more rad in marrow total dose had significantly increased risks of myeloma. These individuals were 20 to 59 years of age at time of exposure and their excess risk became apparent only after a latent period of 20 years or greater.[49] Atomic bomb survivors have had elevated serum immunoglobulin levels[46] and chromosome aberrations in B lymphocytes,[62] which may represent subclinical markers of multiple myeloma risk.

Studies on the mortality experience of radiologists and nuclear processing plant employees have provided information on the risk of occupational exposures to radiation. Lewis[69] observed five multiple myeloma deaths among 425 American radiologists who died between 1948 and 1961 ($P = 0.004$). Whether this excess was solely attributable to radiation exposure is uncertain since other factors may have contributed to the risk.[69] Matanoski et al. also found excess deaths of myeloma among approximately 6,500 radiologists who were followed from 1920 to 1969 and hypothesized that long-term, low-dose exposure may have had an etiologically related immunosuppressive effect.[82] To examine the relationship between dose levels and risk of myeloma, she evaluated the mortality experience of the radiologists from early periods of practice, when radiation exposures were high, and those whose entry period was more recent, when exposures should have been lower. No increased myeloma risk was seen for radiologists who entered practice in the early time period; however, leukemia risk was high for this group. In contrast there was a two-fold excess of myeloma among those who entered practice more recently, supporting the conclusion that long-term exposure to low levels of external radiation is a risk factor for myeloma.[81]

Excess multiple myeloma mortality has

been reported among male employees engaged in plutonium manufacturing at the Hanford Works. Mancuso et al. observed 11 myeloma deaths when 7.6 were expected. However, only eight of these workers were exposed to radiation.[77] Reanalysis of these data by Darby and Reissland revealed that there was an excess of myeloma by two to three deaths for those workers whose total dose was 5 rem or greater 10 years previous to death.[26] Four cases of myeloma occurred among workers at the Windscale Nuclear Processing Plant in Great Britain over the years 1950 to 1974. Only three of these workers were exposed to radiation, two of whom had accumulated doses of 4 and 3.3 rem, respectively, and one of whom had worked with plutonium. Retired and ex-workers were not included in the study; thus an underestimate of the occurrence of myeloma in this population may have taken place.[32]

Familial and Genetic Factors

Genetic factors, as discussed above, appear to contribute to racial and ethnic variation in myeloma occurrence. Familial Occurrence is well documented and a recent review documents that the median age and sex ratio of the 75 reported familial cases resemble those of nonfamilial cases.[10] Siblings are affected 70 percent of the time, suggesting recessively inherited susceptibility,[85] although underascertainment of cases in earlier generations is likely.

Among cases in the same family, the heavy-chain types were usually different, while in 80 percent of cases the light-chain type was the same. This pattern of concordance for light chains may be genetically determined.[10] In addition, although based on small numbers, there was an imbalance of the κ to λ ratio for IgG myeloma in familial cases compared to the general population, which may reflect an altered antibody repertoire in familial cases.

Benign monoclonal gammopathy has been reported occasionally in the relatives of myeloma cases.[66,143] Nevertheless, some myeloma-prone families have had clinically normal relatives with benign M-spikes, suggesting that a variant of familial myeloma is associated with paraproteinemia.[78,87,133] Axelsson and Hallen,[4] in a population-based survey of 6,994 sera from rural Sweden, uncovered three families with benign monoclonal gammopathy in close relatives, including sibs in two families. Williams et al.[134] also reported that probands with BMG have an increased number of relatives with BMG, as compared to control families.

Several studies have also suggested that polyclonal immunoglobulin levels are increased among the close relatives of myeloma cases.[37,94] In some myeloma-prone families, other lymphoproliferative neoplasms have been described, including giant follicular lymphoma, with an immunoglobulin M (IgM) paraprotein, CLL, and mycosis fungoides.[43,120,137]

In contrast to myeloma, the relatives of patients with WM seem to have a plethora of immunologic abnormalities, including an excess of polyclonal IgM, benign IgM-spikes in close relatives, various autoantibodies, and subclinical immune defects.[9,39,41,59] The vast majority of serum M-spikes (12 of 15) in normal family members are IgM, concordant with the heavy-chain type of the proband. Long-term follow-up of one family documented the malignant transformation in two relatives of one family.[38] The predominant light-chain type, as in familial myeloma, is κ (only 5 of 25 were λ).[10] Kalff and Hijmans[59] studied 353 relatives of 23 WM patients and reported seven benign M-spikes—five were IgM—which clearly exceeded expectation. In contrast to myeloma, where all classes of immunoglobulins seem elevated in first-degree relative~the polyclonal increases in WM were confined to the IgM class.[41,59,117]

Seligmann et al.[117] reported a high frequency of rheumatoid factor (an IgM autoantibody) in patients with WM and in their relatives compared to healthy control subjects, especially for the group under 60 years of age.

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Genetic marker studies have been generally unrevealing for the gammopathies. The frequency of human leukocyte antigens (HLA) of the "4C" group seems slightly increased in myeloma.[8,55,79,84] Smith et al.[119] also suggested an association of W-22 with κ-chain myeloma and A-9 with immunoglobulin A (IgA) myeloma, but the numbers were small. A three- to four-fold excess of antigens A28 and B27 in myeloma was reported by Tananov.[124] Ludwig and Mayr[75] recently reported an excess of HLA-B5 in their population from Austria. Genetic determinants of BMG are also suggested by the relationship to certain HLA types[108,128,142] and by the predominance of the IgG-1 subclass.[102]

For WM linkage to the HLA type A-2, B-8, DRW3 was reported in a familial cluster of macroglobulinemia and immunologic abnormalities.[14] These individuals also had positive reactions for the B-cell allo-antigens Ia 172 and 350, previously reported in patients with the lymphoma-prone sicca syndrome.[92] The constellation of lymphoproliferative and autoimmune disorders in this family may result from a heritable abnormality in the immunoregulation of B lymphocytes. The linkage of this abnormality to Ia antigens suggests that a defective immune response gene may predispose to lymphoproliferation or autoimmunity.

The cytogenetic abnormality of greatest etiologic relevance to multiple myeloma is the 14q+ abnormality (see Chapter 26). Wurster-Hill et al.[142] reported the first examples of this abnormality in cases of plasma cell leukemia and multiple myeloma, a finding subsequently confirmed by Philip[100] in an immunoglobulin G (IgG)-λ-myeloma case. Philip and Drivsholm[101] described three additional 14q+ cases and Liang et al.[70] described 6 of 18 with this abnormality associated with accelerated disease and high serum paraprotein level. Although the 14q–t abnormality has not been found in every case of multiple myeloma, the pattern suggests that a common cytogenetic abnormality may play a role in the pathogenesis of various B-cell neoplasms, and this may have a biological basis since human immunoglobulin genes have recently been assigned to this chromosome.[22] Dalla-Favera et al.[25] defined a translocation in Burkitt's lymphoma involving the transfer of the human onc gene, c-myc, to a position juxtaposed to the heavy- or light-chain genes of chromosomes 14 (heavy chain), 2 (κ-light chain), or 22 (A-light chain). Cytogenetic studies of WM have in general been unrevealing.[70]

Role of Chronic Antigenic Stimulation

Clinical reports have suggested that myeloma or macroglobulinemia may occur more often among persons with diseases associated with chronic antigenic stimulation. but epidemiologic confirmation is generally lacking.[11] These primarily anecdotal reports have described myeloma in allergic patients repeatedly hyposensitized[50,54,98,111,129] and in patients with chronic biliary tract disease.[51,54,65,114,115] Among patients with hereditary spherocytosis, which predisposes to chronic biliary tract disease, a high prevalence of IgA myeloma was seen.[115] In a follow-up study of 136 women with sicca syndrome, 7 developed non-Hodgkin's lymphoma, and 3 WM.[63]

In family studies, autoimmune disorders have been reported to occur in the close relatives of patients with WM.[14,117] Hamaker et al.[47] described a 48-year-old man who developed plasmacytoma in the cutaneous pocket where a silastic-covered pacemaker was implanted, a possible counterpart to the plastic-induced plasmacytoma in the BALB/c mouse. Seligmann et al.[118] reported a patient with myeloma that reacted specifically with the a-2 macroglobulin of the horse. The 30-year latent period between sensitization to antitetanus horse serum and myeloma argues for a two-hit mutation model, the first hit leading

to a premalignant monoclonal B-cell proliferation, and the second causing neoplastic growth of a susceptible subclone.[112] In a population-based study from Finland, the incidence of lymphoproliferative neoplasms, including myeloma, was higher in patients with rheumatoid arthritis than in the general population.[52] If chronic stimulation by a specific antigen predisposes to malignancy in the responding clone, then malignant M-spikes with definable antigenic activity should be identified, especially against common types of bacterial or other antigens. Single cases suggesting such a mechanism have been reported infrequently.[60,118] These findings suggest that chronic antigenic stimulation may act as a promoting factor to enhance clonal expansion of cell populations susceptible to malignant transformation to myeloma.

CONCLUSIONS

The cause(s) of multiple myeloma and related dyscrasias are unknown. The major risk indicator is old age. An age-dependent loss of regulatory cell function may be involved, thereby increasing the pool of terminally differentiated, immunoglobulin-secreting cells potentially available for malignant transformation.[103]

The striking predisposition of blacks to myeloma suggests genetic susceptibility, although environmental factors probably also contribute to risk. The elevated risk in blacks may be correlated with their higher baseline immunoglobulin levels.[18] In addition, differences in regulatory cell function may alter the balance of precursor and terminally differentiated B-lymphocytes. In Japan, there is an unusual predominance of T-cell malignancies with a relative deficit of mature B-cell forms. The upward trend in myeloma among blacks suggests that environmental exposures may be involved, in addition to improvements in diagnosis. Further studies are needed to evaluate leads to immunogenetic factors and environmental exposures, including radiation and occupational chemicals. It is possible that some agents may act through antigenic stimulation or suppression of immunoregulatory function.

Genetic factors are likely to account for racial and ethnic patterns. Family studies have been of interest, particularly in uncovering subclinical immunopathy in relatives. The overlap between immunodeficiency and autoimmunity in plasma cell dyscrasias, particularly WM, suggests that a widespread defect in immunoregulation may be involved. The role of chronic antigenic stimulation, perhaps by increasing the size of the clone at risk of plasma cell neoplasia, is suggested by several clinical observations. Clarification of causes of myeloma and related disorders is likely to emerge as analytic epidemiologic studies provide etiologic clues and molecular studies clarify mechanisms of transformation.

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