The Incidence and Epidemiology of Plasma Cell Neoplasms

Daniel Bergsagel

Ontario Cancer Institute/Princess Margaret Hospital. Department of Medicine. Toronto. Ontario. Canada

Key Words. Myeloma • Macroglobulinemia • Monoclonal gamrnopathy of undetermined significance • Prevalence • Incidence • Age • Race • Predisposing factors

Abstract. Plasma cell neoplasia includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), and Waldenstrom's macroglobulinemia (WM). In MGUS, a large, stable clone does not cause symptoms; additional change(s) **is/are** required to convert this clone into a progressively expanding tumor that becomes symptomatic, **as** in MM or WM. The prevalence of MGUS (i.e., the number of cases in a defined population at a certain time) is 20 times greater than MM. The incidence (i.e., the number of cases developing in a defined population in a defined period) has not been determined for **MGUS.** Between **1960** and 1969, the average. annual, age-adjusted **(1950** standard) incidence of MM in Malmö, Sweden was $3.4/10^5$. The incidence of MM is strongly influenced by the age and race of the population, and the diagnostic services available.

MM is a disease of old age; it rarely occurs before the age of **40.** The incidence of MM increases rapidly with age, is lowest among the Chinese and Japanese, intermediate among Caucasians in America and Europe. and highest among blacks in the USA. The striking differences in the incidence of MM in different countries appears to be due to racial rather than **env**ironmental differences, since the low incidence among the Chinese and Japanese in Asia has migrated with them to the Bay area of California and to Hawaii. The high incidence of MM in USA black males **($10.8/10^5$)** and females **($7.2/10^5$)** is more than twice the rate for whites in the same regions. A striking increase in MM mortality rates has been noted in many countries between 1968 and 1986. There is much debate about whether this increase is real, or the result of steadily improving case ascertainment.

Epidemiologists have not firmly identified any hazardous materials that increase the risk of developing **MM.** Previous evidence suggesting that radiation and benzene may play a role in the pathogenesis of MM has been greatly weakened by subsequent follow-up studies.

Marked differences in the incidence of spontaneous MGUS in inbred strains of mice, differences in the susceptibility of these mice to the induction of plasmacytomas by the intraperitoneal injection of mineral oil, the racial differences previously mentioned in the incidence of human MM, the association of MM with the HLA Cw2 allele, and the familial occurrence of MGUS, MM and WM, suggest that genetic factors are important in the genesis of plasma cell neoplasms. Chronic antigenic stimulation (CAS) has long been thought to play a role, but epidemiologic studies have only established an association of MM with rheumatoid arthritis.

Introduction

Plasma cell neoplasms are initiated when an early B cell precursor—with an idiotypic, pre-switch rearrangement of the immunoglobulin gene—undergoes a malignant transformation and proliferates to form a clone [1]. This clone must increase to about 5×10^9 cells before it can produce enough of the monoclonal immunoglobulin to be recognized as a "spike" (M-protein) in a serum electrophoresis pattern. Most subjects with an M-protein are asymptomatic. If other causes of an M-protein can be ruled out. they are labeled as having monoclonal gammopathy of undetermined significance (MGUS). The clone in MGUS is stable. by definition. and the serum M-protein concentration remains on a plateau for many years. However. prolonged follow-up of 241 subjects with MGUS at the Mayo Clinic has shown that about two percent of these patients per year progress to develop multiple myeloma (MM). Waldenstrom's macroglobulinemia (WM). a malignant lymphoma. chronic lymphocytic

Correspondence: Dr. Daniel E. Bergsagel. Department of Medicine, Ontario Cancer Institute/ Princess Margaret Hospital. 500 Sherbourne Street. Toronto. **ONT** M4X 1K9. Canada.

Received September 1. 1994: accepted for publication September 1. 1994. 1066-5099/95/$5.00/0

leukemia or amyloidosis [2]. MGUS is considered to be a premalignant lesion because the clone does not grow progressively. Additional neoplastic change(s) is/are required to convert this large. stable clone into a progressively expanding tumor with malignant characteristics. such as MM or WM.

Prevalence and Incidence

The prevalence of MGUS and MM (i.e., the number of cases in a defined population at a certain time) in the Varmland district of Sweden in 1964. and the incidence (i.e., the number of cases developing in a defined population over a defined period of time) of MM in Malmo. Sweden from 1960-69. ire shown in Table 1. The prevalence of these diseases was determined by doing a serum electrophoresis on 6,995 consecutive adult blood donors over the age of 25. in the spring of 1964 [3]. An M-protein was detected in the sera of 64 individuals (0.9 percent). Only one of this group had MM; 63 were classified as MGUS. Among the 6.931 subjects without serum M-proteins in 1964. two were diagnosed as MM (one had light chain MM) within three years [4]. The population of Varmland in 1964 was about 10,000. In the 70 percent of the adult population of this district who had a serum electrophoresis done in the spring of 1964, the prevalence of MGUS was $901/10^5$, and of MM $43/10^5$. MGUS is encountered much more frequently than MM because these subjects are well. and in contrast to MM patients, who have a median survival of only 32 months from the onset of treatment, MGUS patients tend to survive for prolonged periods, and thus accumulate in the population.

The incidence of MGUS has not been determined. The average. annual. age-adjusted (1950 standard) incidence of MM in Malmo. Sweden was $3.4/10^5$ [5]. In the USA, MM incidence data has been provided by the Surveillance. Epidemiology and End Results (SEER) program since 1973. For the 1973-77 period. the average. annual. age-adjusted (1970 standard) incidence rates per 100.000 for all races was 3.9 for both sexes. 4.7 for males and 3.3 for females [6].

The frequency of MM in a population is strongly influenced by age. race and accessibility of good diagnostic facilities.

Age

The age-specific incidence rates for Malmo. Sweden, 1970-79. are shown in Figure 1. MM was not detected in patients under the age of 40 in this sample. Thereafter the incidence rose progressively with age. to reach $64.5/10^5$ in males. and $36.6110'$ in females over the age of 80 years [5]. The frequency of MGUS also increases with age (Table II).

Race

The average. age-adjusted (world standard population) incidence of MM from selected, population-based cancer registries around the world ranges from 0.5 in Hawaiian Japanese males to 8.2 in USA Bay area black males. per 100.000 person years. The incidence of MM is distinctly lower ($1.4/10^5$, or less) for the Chinese of Shanghai and Singapore, and the Japanese of Osaka and Hawaii. than in the Caucasian populations of North America and Europe.

Comparisons between incidence rates from cancer registries in different countries must be made cautiously. since the populations served may vary in terms of the availability of diagnostic services, the completeness of case ascertainment, and the calculation of age-adjusted incidence rates. Still, there do appear to be real differences in the incidence of MM in different races. The observation that the incidence of MM. age-adjusted to the 1970 U.S. standard. in male Chinese ($2.3/10^5$) and Japanese ($1.7/10^5$) living in San Francisco-Oakland and Hawaii is distinctly lower than for white males ($4.6/10^5$) in these same regions supports this view [7]. Furthermore. the MM incidence rates for blacks in America are more than double the rates for whites. at

Table I. Prevalence and incidence of MGUS and MM in Sweden

Disease [Reference]	No./Total	Prevalence. 1964 per 100.000	Incidence. 1960-69 per 100,000
MGUS [3]	6416995	901	?
MM [4, 5]	316995	43	3.4

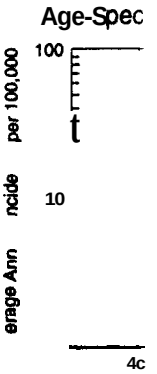

Fig. 1. Average of multiple my Rates ape-adju tion and the Eu brackets): male sexes 3.1 (4.3)

$10.8/10^5$ for b females [8]. T blacks makes ical malignan United States

The prev subjects over communities III) [10]. The Japan is simil in this coun immunoglob nephelometry vation that, fo were signif Japanese. Thi mitted for e Veterans Adı

Table II. The

Author [Refer
Axelsson et al
Englisová et a
Radl et al. [55

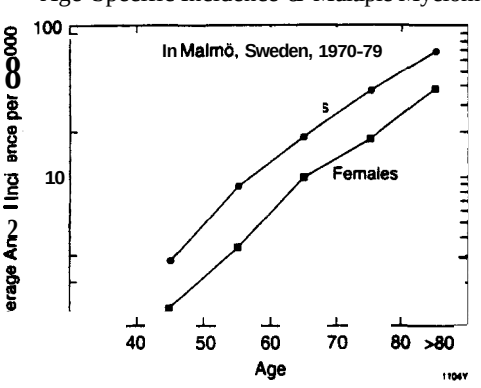

Fig. 1. Average. annual. age-specific incidence rates of multiple myeloma in Malmo. Sweden. 1970-1979. Rates age-adjusted to the 1950 U.S. (total) population and the European standard population (values in brackets): males 4.6 (6.2); females 2.2 (3.0); and both sexes 3.2 (4.3)[5].

$10.8/10^5$ for black males and $7.2/10^5$ for black females [8]. The increased incidence of MM in blacks makes this the most common hematological malignancy in the black population of the United States [9].

The prevalence of MGUS is also lower in subjects over the age of 60 living in retirement communities in Japan than in the U.S. (Table III) [10]. The reduced prevalence of MGUS in Japan is similar to the lower incidence of MM in this country. Measurements of normal immunoglobulins in these subjects by laser nephelometry provided the surprising observation that, for unknown reasons, IgG and IgA were significantly higher in the elderly Japanese. The frequency of MGUS in sera submitted for electrophoresis at the Houston Veterans Administration Hospital was found to be much higher in blacks than in whites. especially in the group over the age of 79 [11]. again in agreement with the higher incidence of MM in blacks.

Increasing Mortality Rates for MM

Trends in the MM mortality rates for four age groups in the U.S. between 1968 and 1986 are shown in Figure 2. A striking increase in these rates occurred during this period. especially in the older age groups [12]. Similar increases were noted in the reported. MM death rates from the United Kingdom. France. Germany, Japan and Italy [12. 13]. The rate of increase in the MM mortality rate is greatest in the group over the age of 85. and falls continuously with decreasing age. The rate of increase is substantial by the age of 70. more than doubling in both sexes and in all countries between 1968 and 1986. There is much debate about whether the increasing mortality rate from MM is real. or the result of steadily improving case ascertainment.

The fact that this marked increase in the MM mortality rate has not been observed in three communities with a high standard of medical care and a long interest in MM (Olmstead County, Minnesota: Malmo, Sweden and the canton of Vaud, Switzerland) suggests that the rising MM mortality rates in other parts of the world are largely due to improving case ascertainment [5, 14-16]. *Kyle et al.* [16] attribute their failure to detect an increase in the incidence of MM in Olmstead county between 1945 and 1990 to the fact that the Mayo Clinic provides most of the medical care in this county. Hematologists and epidemiologists at the Mayo Clinic have long had a major interest in MM. and it seems likely that they have succeeded in detecting. and accurately diagnosing. almost all of the cases of MM during the 45-year study period.

Table II. The prevalence of MGUS increases with age

Author [Reference]	Age group	MGUS/Total	Percent
Axelsson et al. [3]	30-49	5/2826	0.2
	50-69	401293I	1.4
	70-89	191735	2.6
Englisová er *al.* [54]	≥90	5/26	19.2
Radl et al. [55]	≥95	14/73	19.2

Table III. The prevalence of MGUS is lower in Japan than in the United States

		Prevalence of MGUS in subjects over age 60 in retirement communities		
Country		MGUS/Total	mg/ml	Percent
Japan		4/146		2.7
	Normal IgG		.685 ± 520	
	Normal IgA		283 ± 116	
United States		11/111		10.0
	Normal IgG		.118 ± 402	
	Normal IgA		226 ± 116	

From [10].

What Causes Plasma Cell Neoplasia?

The short answer to this question is that we don't know! Epidemiologists are still in the process of searching for clues. The major tools these detectives use are studies of cohorts. and comparisons of the exposures of cases and controls [17].

In a cohort study, defined populations exposed to factors suspected of increasing or decreasing the incidence of a cancer. and an unexposed control group (which should be as much like the exposed group as possible) are followed for an interval long enough for a number of cancers to develop. The incidence of cancer in the exposed and control groups is then compared. A cohort study is often the first broad-range attempt to detect an exposure that may be involved in the pathogenesis of a cancer. Suspicious exposures are then investigated in more detail. perhaps with the aid of a hypothesis about the biologic mode of action of the agent in question. These studies require very large numbers of subjects, and prolonged observation, in order to have a reasonable chance of detecting a change in the incidence of cancer following exposure. Cohort studies are not very sensitive, and are rarely specific enough to identify the causative agent.

Case-control studies begin with a group of patients with a malignancy e.g., myeloma. and compare the exposure of these cases to various agents with the exposure of a control group. selected to match the cases in terms of important confounding variables such as age. race. sex. socioeconomic factors. smoking, etc. The exposure in question is assessed by a questionnaire administered to both the cases and controls. These studies can be done quickly, and require fewer subjects to detect a given level of risk. However, they are dependent on the ability of the cases and controls to remember their exposures equally well. There are also many potential biases in the selection of cases and controls, and in the measurement of exposure.

Riedef et *al.* [9] have summarized all of the reported positive associations between occupational exposures and MM. Agricultural employment (predominantly farming) is the occupation most frequently associated with MM. Most studies have detected this association. but some, including a recent large (1.222 cases and 4.888 controls) case-control study of occupational risk factors for MM in Danish men [18], have not. However. none of these studies have been able to identify the aspect of agricultural work. be

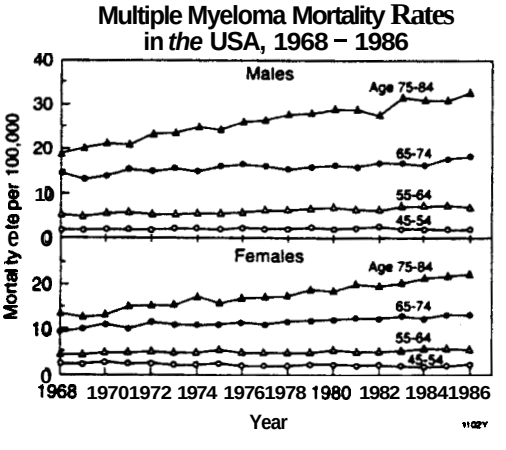

Fig. 2. Myeloma mortality rates per 100,000 for four age groups in the USA for 1968-1986 [I?].

it contact with animals, grains. dust. fertilizers, pesticides or engines, which increases the risk of farmers for MM.

lnstead of reviewing the rather weak associations, and inconsistent results of most cohort and case-control studies of occupational and environmental risk factors for MM, 1 propose to first examine the role of exposure to two agents, radiation and benzene, which were at one time thought to be important in the pathogenesis of MM. Finally. I will consider the evidence that genetic factors and chronic antigenic stimulation are involved in the genesis of plasma cell neoplasia.

Radiation

An excess frequency of MM has been observed in some populations exposed to radiation, including American radiologists [19], workers in nuclear facilities [20, 21], atomic bomb survivors [22], thorotrast patients [23], radium-dial painters [24] and others [25]. An analysis of causes of death among the atomic bomb survivors in Japan [22] was, for a time. thought to provide strong evidence for an association between radiation dose and the incidence of MM. This database has recently been reanalyzed, using only primary cases of MM diagnosed among residents of Nagasaki and Hiroshima, who were in these cities at the time of the bomb, and had Dosimetry System 1986 estimates of between 0 and 4 Gy kerma [26]. This new analysis found no evidence of an excess risk of MM in the atomic bomb survivors. Because this negative result differs sharply from the earlier positive association reported in mortality analyses based on death certificates [27], and an earlier incidence study [22], the data was analyzed several different ways, in an effort to explain the reasons for the different result. The change is thought to be due primarily to increased follow-up, adding 12 years. But differences in diagnostic criteria, and the decision to consider only first-primary MM. also affected the risk estimates. The decision to limit the analyses to the cohort with DS86 kerma estimates below 3 Gy did not have a major impact on the findings.

Benzene

Case reports of MM developing in Turkish patients who had been heavily exposed to benzene suggested that this agent might be involved in the pathogenesis of the disease [28]. A cohort analysis of workers (predominantly white males) employed in the manufacture of rubber hydrochloride in pliofilm plants, by a process that includes the dissolution of natural rubber in benzene. is one of the best studies of benzene-exposed workers. This cohort has been analyzed on four occasions by the National Institute for Occupational Safety and Health. In the analyses of 1977 and 1981, an increased risk of acute myelogenous leukemia was recognized. but there was no increase in the incidence of MM [29, 30]. In the third analysis of 1987. four cases of MM were detected [31]. The expected number of MM deaths in an unexposed population of the same age. sex and race was one. However, three of the workers who developed MM in this study had minimal exposure to benzene (one had worked at the plant for only four days), and there was no trend towards an increasing incidence of MM with greater exposure. A fourth update has added six years of follow-up [32]. No new cases of MM have developed. and the standardized mortality ratio for MM now is no longer significantly increased in the benzene-exposed group.

Genetic Factors

Striking differences in the incidence of monoclonal gammopathies in inbred strains of mice. racial differences in the incidence of MGUS and MM in humans. the association of an increased risk of developing MM with certain human leukocyte antigens (HLA), and the occurrence of familial MGUS. MM and monoclonal macroglobulinemia all suggest that genetic factors play an important role in the pathogenesis of plasma cell neoplasms.

Plasma Cell Neoplasia in Inbred Strains of Mice

Benign monoclonal pammopathies. closely resembling the MGUS found in humans. develop spontaneously in various inbred strains of mice (Table IV). The C57BL/Ka variety has been studied extensively [33]. A monoclonal gammopathy (usually IgG) can be detected in about three percent of these mice by three months of age. The frequency increases to more than 60 percent of mice who live to 24 months. A characteristic M-protein persists for the life of the mouse, but additional M-proteins can appear in the same mouse. The frequency of

Table IV. Mouse plasma cell neoplasms

	Major Ig	Frequency	
A. Spontaneous monoclonal gammopathies [Reference]		3mo.	24 mo.
CBA [33]		0	1%
BALB/c [33]		0	t0%
SZB [33]	IgM	0	26% 18 mo.
C3H [33]	IgM	0	36%
C57BL/Ka [33]	IgG	3	>60%
Sude [35]		0	75%
B. Mineral-oil induced plasmacytomas [56]			
BALB/c	IgA		62.54
NZB			20-304
C57BL			Rare
DBA/2			Rare
C3H			Rare
AL/N			Rare

multiple M-proteins increases with age. Few of the monoclonal gammopathies progress to become malignant tumors, but ***Radl et al.*** [34] have shown that a few old mice do develop M-protein-secreting tumors. which can be transplanted by the intravenous injection of bone marrow cells. Most of these transplantable tumors cause osteolytic lesions in the recipients. making this a good mouse model of MM. About 75 percent of homozygous nude mice maintained in a sterile environment develop an M-protein (usually IgG) by 24 months [35]. These mice lack a thymus and are T cell deficient. Nude mice raised in a conventional environment develop a monoclonal IgM at an earlier age. Only 47 percent of the heterozygous littermates of the nude mice developed M-proteins. In contrast, 26 percent of NZB mice. and 36 percent of C3H mice develop an IgM monoclonal gammopathy by 24 months. whereas in DBA and BALB/c mice, spontaneous M-proteins are uncommon. These observations indicate that the incidence and type of spontaneous M-protein in inbred strains of mice are influenced strongly by the mouse genotype. The specific genes have not been identified yet.

Plasmacytomas can be induced in some strains of mice by the intraperitoneal injection of mineral oil (Table IV). It is of interest that susceptibility to the induction of peritoneal plasmacytomas does not correlate with the strains that have a high incidence of spontaneous M-proteins. Again. the genotype influences the frequency of mineral oil-induced plasmacytomas. and the penes involved have not been identified yet.

Racial Differences in the Incidence of MGUS and MM

The striking differences in the incidence of **MGUS** and MM in different parts of the world, mentioned earlier, appear to be due to racial rather than environmental differences, since the low incidence of these disorders among the Chinese and Japanese in Asia has traveled with them to the Bay area of California, and to Hawaii. The genes that determine these racial differences have yet to be identified.

Certain HLA Types Are Associated with an Increased Risk of MM

A large population-based study of 46 black male MM cases (with 88 black male controls) and 85 white male MM cases (with 122 white male controls) has been done to determine whether there is any association of HLAs of Class I (HLA-A, HLA-B, HLA-C) and Class II (HLA-DR, HLA-DQ) with the disease [36]. Black MM patients had significantly higher gene frequencies than their controls for Bw65, Cw2 and DRw14, while white MM cases had higher gene frequencies than controls for A3 and Cw2, and blanks at the DR and DQ loci. The frequency of Cw2 in the black and white controls was similar. These findings suggest that the Cw2 allele. or a gene close to the C loci, confers susceptibility to the development of MM, but does not explain the higher risk among blacks. The authors also suggest that undefined Class II antigens may play an etiologic role. New molecular techniques. using genomic DNA, may lead to the identification of these alleles.

·***Familial Plas***

Several
MM and MG
. families rep
- added two br
[38], and ani
with IgG Mh
and two brot
these 43 fami
in seven first-
spring), was r
relatives (sib
more distant r
one third-de;
fourth-degre
families witt
Renicr et ***al.*** [
second-degre

The occu
nancy in a fa
pattern of inh
may be expos
ard. However.
ognized in an
have been inv
discovery that
have inherite
40, 41] sugge
these plasma c
lod score (the
lihood of link
by the LIPED
of Waldenst
autoimmune
segregating w
some six. The
favoring chro
susceptibility

Chronic Anti

Clinician
about the pos
genesis of MM
stimulates a
immune syste
of the respon
eral attempts t
with a past hi
terial infecti
allergy desens
disease: but th

requency	
).	24 mo.
	1%
	10%
26%	18 mo.
	36%
	>60%
	75%
	67.58
	20-30%
	Rare
	Rare
	Rare
	Rare

nce of MGUS

the incidence
it parts of the
ur to be due to
al differences.
ese disorders
se in Asia has
a of California,
etermine these
identified.

red *with an*

ıdy of 46 black
male controls)
vith 122 white
to determine
ın of **HLAs** of
C) and Class **II**
disease [36].
tly higher gene
or Bw65, Cw?
ses had higher
r **A3** and Cw2,
loci. The fre-
white controls
st that the Cw2
ci. confers sus-
MM. but does
ng blacks. The
d Class **II** anti-
New molecu-
DNA, may lead
les.

Familial Plasma Cell Neoplasia

Several families with multiple cases of MM and **MGUS** have been reported. To the 41 families reported by *Loth et al.* [37] can be added two brothers who developed IgG/k MM [38], and another family in which a female with IgG MM was found to have two sisters and two brothers with IgG **MGUS** [39]. In these 43 families. MM or **MGUS** was detected in seven first-degree relations (parent and offspring), was most frequent in 32 second-degree relatives (siblings).and much less frequent in more distant relatives. with occurrences in only one third-degree (aunt and niece), and three fourth-degree (cousins) relations. In the **25** families with monoclonal IgM reviewed by Renier et *al.* [39], nine were first-, and 16 were second-degree relations.

The Occurrence of multiple cases of a malignancy in a family, without a clear Mendelian pattern of inheritance. suggests that the family may be exposed to the same environmental hazard. However. no hazardous factor has been recognized in any of the M-protein families that have been investigated. On the other hand. the discovery that several affected family members have inherited identical HLA haplotypes [37, **40.** 41] suggests that the tendency to develop these plasma cell neoplasms may be inherited. **A** lod score (the logarithm of the ratio of the likelihood of linkage to no linkage) was calculated by the LIPED program to test if the occurrence of Waldenstrom's macroglobulinemia and autoimmune manifestations in a family was segregating with the **HLA** region on chromosome six. The lod score turned **out** to be 4.86, favoring chromosomal linkage of a postulated susceptibility gene to the **HLA** complex [41].

Chronic Antigenic Stimulation (CAS)

Clinicians have speculated for many years about the possible role of CAS in the pathogenesis of MM [42]. The hypothesis is that CAS stimulates a proliferative response in the immune system. and that MM develops in one of the responding cells. There have been several attempts to correlate the occurrence of MM with a past history of exposure to viral or bacterial infections. immunizations. allergies, allergy desensitization therapy and autoimmune disease: but the results are inconsistent [43].

There does. however. appear to be an **association** between rheumatoid arthritis and MM. At least two follow-up studies of patients with rheumatoid arthritis have detected a subsequent increased incidence of MM [44-46], and an excess of rheumatoid arthritis has been detected in case-control studies in New Zealand and northern Sweden [47, 48]. An examination of the frequency of autoimmune diseases among first-degree relatives of MM patients discovered a significantly increased risk of rheumatoid arthritis, as compared to the incidence in first-degree relatives of the controls [49]. If this finding is confirmed, it will suggest that genetic factors underlie the association.

A case-control study of patients with Gaucher's Disease in Israel found that these patients have an increased risk of developing hematologic malignancies. including MM [50]. A possible mechanism is that the accumulating cerebroside acts as a chronic antigenic stimulant of the immune system. as was first suggested by *Shoenfeld* et *al.* [51]. These investigators found that patients with Gaucher's Disease had elevated levels of serum immunoglobulins. that increased with age. In addition. *Marti* et al. [52] detected diffuse, polyclonal hyperglobulinemia in 10. oligoclonal hyperglobulinemia in six. and **MGUS** in two of 23 patients with Gaucher's Disease. The sequence may be that **CAS** leads to a polyclonal, followed by an oligoclonal response, from which a monoclonal proliferation emerges. resulting in MGUS. MM. lymphoma or leukemia.

The discovery of an **HIV-**1-seropositive patient with MM. whose IgG/k M-protein specifically recognized the **HIV-**I p24 gag antigen. suggests that the antigen-driven response to this viral infection did play a role in the pathogenesis of MM in this patient [53].

References

1 Bakkus MHC. Vanrict I. Vancamp B et al. Evidence that the clonogenic cell in multiple-myeloma originates from a pre-switched but somatically mutated B-cell. Br J **Haematol** 1994:87:68-74.

2 Kyle RA. Lust JA. .Monoclonal gammopathies of undetermined significance. In: Wiernik PH. Canellos **GP.** Kyle **RA.** Schiffer CA. eds. Neoplastic Diseases of the Blood. Vol I. New

York. Edinburgh. London, Melbourne. Tokyo: Churchill Livingstone. 1991:571-596.

3 Axelsson U. Bachmann R. Hällén J. Frequency of pathological proteins (M-components) in 6.995 sera from an adult population. Acta Med Scand 1966;179:235-247.

4 Axelsson U, Hällén J. A population study on monoclonal gammopathy: follow-up after 5 1/2 years on 64 subjects detected by electrophoresis of 6995 sera. Acta Med Scand 1972;191:111-113.

5 Turesson I. Zettervall O. Cuzik J et al. Comparison of trends in the incidence of multiple myeloma in Malmo. Sweden. and other countries. 1950-79. N Engl J Med 1984;310:421-424.

6 Young JL Jr., Percy CL. Asire AJ. eds. Surveillance. epidemiology. and end results: incidence and mortality data. 1973-77. Bethesda: National Institutes of Health. publication 81-2330. 1981:1082. National Cancer Institute Monograph 57

7 Devesa SS. Descriptive epidemiology of multiple myeloma. In: Obrams GI, Potter M, eds. Epidemiology and Biology of Multiple Myeloma. Berlin: Springer-Verlag, 1991:3-12.

8 Sondik EJ. Cancer Statistics Review 1973-1986. Washington. D.C.: US Government Printing Office. 1989DHHS publication no. NIH 89-2789.

9 Riedel DA. Pottern LM, Blattner WA. Epidemiology of multiple myeloma. In: Wiernik PH. Canellos GP, Kyle RA. Schiffer CA. eds. Neoplastic Diseases of the Blood Vol.I. New York. Edinburgh. London, Melbourne, Tokyo: Churchill Livingston. 1991:347-372.

10 Bowden M. Crawford J. Cohen HJ et al. A comparative study of monoclonal gammopathies and immunoglobulin levels in Japanese and United Stateselderly. J Am Geriatr Soc 1993;41:11-14.

11 Singh J. Dudley AJ. Kulig KA. Increased incidence of monoclonal gammopathy of undetermined significance in blacks and its age-related differences with whites on the basis of a study of 397 men and one woman in a hospital setting. J Lab Clin Med 1990;116:785-789.

12 Davis DL. Hoel D. Fox J et al. International trends in cancer mortality in France. West Germany. Italy. Japan. England and Wales. and the United States. Ann NY Acad Sci 1990;609:5-48.

13 Schwartz J. Multinational trends in multiple myeloma. Ann NY Acad Sci 1990;609:215-224.

14 Linos A. Kyle RA. O'Fallon WM et al. Incidence and secular trend of multiple myeloma in Omstead County. Minnesota: 1965-77. J Nat Cancer Institute 1981;66:17-20.

15 Levi F. La Vecchia C. Trends in multiple myeloma [letter]. Int J Cancer 1990;46:755-756.

16 Kyle RA. Beard CM. O'Fallon WM et al. Incidence of multiple myeloma in Olmstead County. Minnesota: 1978 through 1990. with a review of the trend since 1945. J Clin Oncol 1994;12: 1577-1583.

17 Boyd NF. The epidemiology of cancer: In: Tannock IF. Hill RP. eds. The Basic Science of Oncology (Second Edition). Toronto: Pergamon Press. 1992:7-22.

18 Heineman EF. Olsen JH. Pottern LM et al. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control 1992;3:555-568.

19 Lewis EB. Leukemia. multiple myeloma and aplastic anemia in American radiologists. Science 1963;42:1492-1494.

20 Dolphin GW. A comparison of the observed and expected cancers of the haematopoietic and lymphatic systems among workers at Windscale. London: Her Majesty's Stationery Office. 1976.

21 Gilbert ES. Omohundro E, Buchanan JA et al. Mortality of workers at the Hanford site: 1945-1986. Health Phys 1993;64:577-590.

22 Ichimaru M. Ishimaru T, Mikami M et al. Multiple myeloma among atomic bomb survivors. Hiroshima and Nagasaki. 1950-76. N Engl J Med 1979;301:439-440.

23 Faber M. Malignancies in Danish thorotrast patients. Health Phys 1978;35: 153-158.

24 Poledenak AP. Stehney AF, Rowland RE. Mortality among women first employed before 1930 in the U.S. radium dial painting industry. A group ascertainment from employment lists. Am J Epidemiol 1978;107:179-195.

25 Cuzick J. Radiation-induced myelomatosis. N Engl J Med 1981;304:204-210.

26 Preston DL. Kusumi S. Tomonaga M et al. Cancer incidence in atomic-bomb survivors. Part III: Leukemia. lymphoma and multiple-myeloma. 1950-1987. Radiat Res 1994;137(suppl 2):S68-S97.

27 Shimizu Y, Kato H. Schull WJ et al. Life Span Study Report 11. Part I. Comparison of risk coefficients for site-specific cancer mortality based on the DS86 and T65DR shielded kerma and organ doses. Radiat Res 1989;118:502-524.

28 Aksoy M. Erdem S. Dincol G et al. Some etiologic factors in the etiology of multiple myeloma. A study in 7 patients. Acta Haematol 1984;71:116-120.

29 Infante P
Leukemi
1977;ii:7

30 Rinsky R
benzene

31 Rinsky R.
and leuke
N Engl J

32 Paxton M
Leukemia
the pliofil
sure distri

33 Radl J. H
Idiopathic
model –
Journal of

34 Radl J. Cr
model of h
J Pathol 19

35 Radl J. Mir
frequency
the sera of
Immunopar

36 Pottern L
multiple m
evidence
Epidemiol

37 Loth TS.
aspects of
1991;156:4

38 Bizzaro N.
tiple myel
undeterm
Haematolg

39 Renier G. I
ers with W
Cancer 198

40 Grosbois
Multiple m
chemical a
Cancer 198

41 Blattner W
Waldenstr
mune dise
1980;93:83

42 Isobe T. O
associated w
806 cases. A

43 Riedel DA.
multiple m
Am 1992;6:

29 Infante PF. Rinsky RA. Wagoner JK et al. Leukemia in benzene workers. Lancet 1977;ii:76-78.

30 Rinsky RA. Young RJ. Smith AB. Leukemia in benzene workers. Am J Ind Med 1981;2:217-245.

31 Rinsky RA. Smith AB. Hornung R et al. Benzene and leukemia: an epidemiologic risk assessment. N Engl J Med 1987;316:1044-1050.

32 Paxton MB. Chinchilli VM. Brett SM et al. Leukemia risk associated with benzene exposure in the pliofilm cohort: I. Mortality update and exposure distribution. Risk Anal 1994;14:147-154.

33 Radl J. Hollander CF. Van den Berg P et al. Idiopathic paraproteinemia. I. Studies in an animal model – the aging C57BL/KaLwRij mouse. Journal of Exp Immunol 1978;33:395-402.

34 Radl J. Croese JW. Zurcher C et al. Animal model of human disease. Multiple myeloma. Am J Pathol 1988;132:593-597.

35 Radl J. Mink JG. van den Berg P et al. Increased frequency of homogeneous immunoglobulins in the sera of nude mice with age. Clin Immunol Immunopathol 1980;17:469-476.

36 Pottern LM. Gart JJ. Nam JM et al. HLA and multiple myeloma among black and white men: evidence of a genetic association. Cancer Epidemiol Biomarkers Prev 1992;1:177-182.

37 Loth TS, Perrotta AL, Lima J et al. Genetic aspects of familial multiple myeloma. Mil Med 1991;156:430-433.

38 Bizzaro N, Pasini P. Familial occurrence of multiple myeloma and monoclonal gammopathy of undetermined significance in 5 siblings. Haematolgica 1990;75:58-63.

39 Renier G. Ifrah N. Chevailler A et al. Four brothers with Waldenstrom's macroglobulinemia. Cancer 1989;64:1554-1559.

40 Grosbois F, Gueguen M. Fauchet R et al. Multiple myeloma in two brothers. An immunochemical and immunogenetic familial study. Cancer 1986;58:2417-2421.

41 Blattner WA. Garber JE. Mann DL et al. Waldenstrom's macroglobulinemia and autoimmune disease in a family. Ann Intern Med 1980;93:830-832.

42 Isobe T. Osserman EF. Pathologic conditions associated with plasma cell dyscrasia: a study of 806 cases. Ann NY Acad Sci 1971;90:507-518.

43 Riedel DA. Pottern LM. The epidemiology of multiple myeloma. Hematol Oncol Clin North Am 1992;6:225-247.

44 Isomaki HA. Hakulinen T. Joutsenlahti U. Excess risk of lymphomas. leukemia and myeloma in patients with rheumatoid arthritis. J Chron Dix 1978;31:691-696.

45 Katusic S. Beard CM. Kurland LT et al. Occurrence of neoplasms in the Rochester. Minnesota. rheumatoid arthritis cohort. Am J Med 1985;78(1A):50-55.

46 Hakulinen T. Isomaki H. Knekt P. Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. Am J Med 1985;78(1A):29-32.

47 Pearce NE. Smith AH. Howard-JK et al. Case-control study of multiple myeloma and farming. Br J Cancer 1986;54:493-500.

48 Eriksson M. Rheumatoid arthritis as P risk-factor for multiple myeloma: a case-control study. Eur J Cancer 1993;29A:259-263.

49 Linet MS. McLaughlin JK. Harlow SD et al. Family history of autoimmune disorders and cancer in multiple myeloma. Int J Epidemiol 1988;17:512-513.

50 Shiran A. Brenner B. Laor A et al. Increased risk of cancer in patients with Gaucher's disease. Cancer 1993;72:219-224.

51 Shoenfeld Y. Gallant LA. Shaklai M et al. Gaucher's disease: a disease with chronic stimulation of the immune system. Arch Pathol Lab Med 1982;106:388-391.

52 Marti GE. Ryan ET, Papadopoulas NM et al. Polyclonal B-cell lymphocytosis and hyperglobulinemia in patients with Gaucher disease. Am J Hematol 1988;29:189-194.

53 Konrad RJ. Kricka LJ. Goodman DRP et al. Brief report: myeloma-associated paraprotein directed against the HIV-I p24 antigen in an HIV-1-seropositive patient. N Engl J Med 1993;328:1817-1819.

54 Englisova M. Englis M. Kyral V et al. Changes in immunoglobulin synthesis in old people. Exp Geront 1968;3:125-127.

55 Radl J, Sepers JM, Skvaril F et al. Immunoglobulin patterns in humans over 95 years of age. Clin Exp Immunol 1975;22:84-90.

56 Potter M. Experimental plasma cell tumors and other immunoglobulin-producing lymphoreticular neoplasms in mice. In: Azar HA. Potter M. eds. Multiple Myeloma and Related Disorders Vol I. Hagerstown. Maryland: Harper & Row. 1973:153-194.