2 Epidemiology of Multiple Myeloma and Related Disease

Brian G. M. Durie, MD

CONTENTS

1. INTRODUCTION

Plasma cell disorders include monoclonal gammopathies of undetermined significance (MGUS), smoldering/indolent myeloma, and active myeloma. Related disorders are Waldenstrom's macroglobulinemia, the heavy-chain diseases, primary systemic amyloidosis, and systemic light-chain deposition disease. The characteristic feature of these diseases is the involvement of cells that are either plasma cells or lymphocytes resembling plasma cells and typically the production of immunoglobulin (Ig) (heavy and/or light chains) in a monoclonal fashion. The most common myelomas are IgG or IgA κ or λ, and κ or λ Bence Jones-only myeloma. Waldenstrom's macroglobulinemia is IgM κ or λ in type.

There is an abundance of evidence *(1)* supporting the view that the malignant transformation in multiple myeloma (MM) occurs at a late stage of B-cell ontogeny

From: *Current Clinical Oncology: Biology and Management of Multiple Myeloma*
Edited by: J. R. Berenson

that precedes differentiation to the mature plasma cell, i.e., the target cell subject to malignant transformation has already been committed by antigen to the production of monoclonal IgG (κ/λ) or IgA (κ/λ), or IgM (κ/λ) in the case of Waldenstrom's macroglobulinemia. The mutation/recombination gene translation rates in antigen-driven B-cell differentiation have been variously estimated to be a million-fold higher than in somatic cells *(2)*. Therefore, the occurrence of a transforming event that can eventuate in MM over the life span of B cells is a statistical reality. Studies of plasmacytomas in mice *(3)* have shown that antigenic stimulation is required for these transformation dynamics to occur. Until now, traditional epidemiology has been the major technique used to investigate the causes of this plasma cell transformation process (Fig. 1).

MM accounts for approx 1% of all cancer cases and 10 to 15% of cases of hematologic cancer specifically *(4,5)*. Although the general incidence of MM in the United States is approx 4 to 5 per 100,000, there is broad range of incidence values for different populations, both in the United States and around the world, ranging from 1 per 100,000 or less for most Asians to 9 or more per 100,000 for populations of African origin. The basis for these racial differences is unknown. According to American Cancer Society statistics, the incidence of myeloma increased by 82% during the 1960s through the mid-1980s; the reasons for this are also unknown. The median age of patients at the time of MM diagnosis is approx 65 yr. Data from several institutions and countries around the world reflect the increasing incidence of MM during this century, as well as a decreasing median age at diagnosis *(6,7)*. Nonetheless, myeloma remains a rare disease in individuals younger than 40 yr, with only 3 to 5% of patients falling into this age category. The extent to which a true increase in the incidence of myeloma occurs in individuals aged 40 to 65 yr remains controversial.

2. BASIC DEMOGRAPHIC PATTERNS: INCIDENCE BY COUNTRY, AGE, GENDER, AND RACE

Tables 1 and 2 summarize incidence rates under various conditions. In Table 1, the annual age-standardized incidence rates of MM are summarized by country and by gender as high, intermediate, and low. The consistently higher incidence level in men vs women can be seen across the different groups. The much higher incidence rates for African Americans, Maoris, and Hawaiians, for example, are in sharp contrast with the very low rates for individuals from various parts of Asia, including India, Japan, the Philippines, and China. The intermediate rates are really quite consistent for the majority of the predominantly Caucasian countries, including the United States, Britain, Finland, and Germany. Similar rates apply in most other predominantly Caucasian industrialized nations, including Italy, France, Spain, and Belgium.

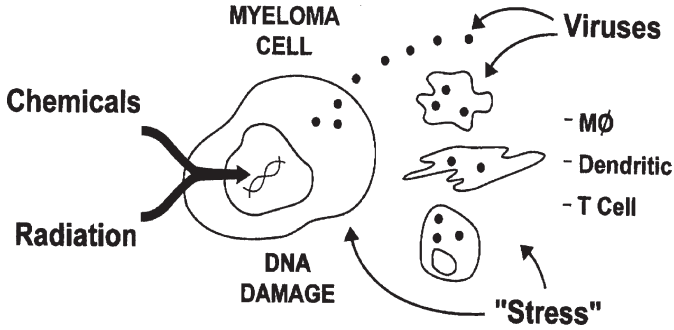

Fig. 1. The four types of causal factors for myeloma are depicted: chemicals (carcinogenic); viruses (oncogenic and/or triggering); ionizing radiation; microenvironmental stress factors (e.g., hypoxia).

Table 1
Annual Age-Standardized Incidence of Multiple Myeloma by Country

High Rates[a]	*M/F*	*Intermediate Rates*[a]	*M/F*	*Low Rates*[a]	*M/F*
US: African American:	10.3/7.1	US: Caucasian:	4.7/3.2	India:	1.8/1.5
New Zealand: Maori	8.4/7.8	Britain:	4.5/3.7	Japan:	2.1/1.6
Martinique:	8.3/8.0	Finland:	4.4/2.8	Philippines:	1.2/1.1
Hawaii: Hawaiian	7.4/5.6	Germany:	3.0/2.4	China:	1.1/0.5

Adapted from ref. *4*.
[a]Incidence per 100,000; listed as male/female (M/F)

Table 2
Annual Incidence of Multiple Myeloma per 100,000 by Age, Gender, and Race

	Age Range	
Race	*55–59 yr*	*75–79 yr*
Caucasian, F/M	0.5/1.0	2.5/4.1
African American, F/M	2.0/2.0	4.5/7.9

Adapted from ref. *(8)*.

The striking effect of age is highlighted in Table 2. The very sharp increase in incidence among individuals aged 55 to 75 yr can be seen with the higher incidence for men vs women and also the substantially higher incidence for African Americans vs Caucasians. Although many explanations have been offered for the impact of age, gender, and race (discussed later in this chapter), more detailed analyses of molecular polymorphisms, human lymphocyte antigen (HLA)

patterns, hormonal influences, and so on, will be required to clarify the biologic basis for these differences.

As highlighted by Schwartz *(6)* and Davis and colleagues *(7)*, analysis of multinational trends in MM can be helpful in assessing the interaction between environmental factors and the inherent predisposition of individuals of different ages, gender, and race. The broad patterns of incidence support the notion that environmental factors influenced the incidence of myeloma during the last 100 years *(8)*. Within that time frame, there has been insufficient opportunity for new generations to manifest any substantial predisposition differences.

3. RADIATION EXPOSURE AND THE RISK FOR MM AND MGUS

Evidence of an association between radiation exposure and the subsequent development of MM and MGUS is summarized in Table 3. It includes the findings of major studies that provide data from nuclear bomb survivors, nuclear facility workers, diagnostic radiation studies, as well as experimental data all indicating that ionizing irradiation can lead to the development of both MM and MGUS. Given the fact that these are relatively rare forms of cancer for which the predisposition varies by age, gender, and race, inconsistencies have been found in reported data. Because the dose and timing of radiation and additional confounding exposures are important, very detailed and careful analyses are necessary to draw any firm conclusions (*see* ref. *9)*.

Nuclear bomb survivors are clearly at increased risk for MM. The association of radiation exposure to myeloma is strongly supported by a mortality study by Shimizu *(10)* and a very recent follow-up analysis by Rabitt-Roff *(11)* of UK veterans exposed to atomic radiation during nuclear tests in the Pacific Ocean. Rabitt-Roff identified 36 individuals who developed MM out of a population of approx 1500 that was exposed to the same radiation. The unique feature of the Rabitt-Roff study is the accurate ascertainment of long-term health effects among participants in nuclear weapons tests. The latency in onset of MM, especially beyond 5–10 yr, was not anticipated. Questions are raised about prior case ascertainment methods and the appropriate denominator to use for such analyses and comparisons. Additional studies are now underway (*see* NRPB web site: www.nrbp.org.uk). Of note, in this regard, follow-up data regarding US experience at Hanford, Washington and other Department of Energy (DOE) sites is available on the DOE web site *(12)*.

The data from nuclear facilities in the United States and the United Kingdom strongly support the assessment that radiation exposure can cause MM in a dose-dependent fashion. Fortunately, Gilbert *(13)* and Smith *(14)* provide information about dosing and the dramatic rise in relative risk increase with dose and duration of exposure. Likewise, Boice *(15)*, in evaluating diagnostic radiation, indicates a clear correlation between the calculated bone marrow dose and the likelihood

Table 3
Radiation Exposure and the Risk for Multiple Myeloma and MGUS

Type of Exposure	*Type of Study*	*Relative Risk*	*Comments*	*Reference*
Nuclear bomb survivors	Japan mortality	3.3	Negative incidence study unexplained	Shimuze et al., 1990 *(10)*
	United Kingdom incidence	36/1500 exposed[a]	Follow-up studies required	Rabbit Roff, 1998 *(11)*
Nuclear facility workers	US nuclear weapons plants mortality	3.3–33	Direct, increasing mortality with dose	Gilbert et al., 1989 *(13)*
	Sellafield, UK mortality	1.2–5.0	Increasing risk with higher exposure	Smith et al., 1986 *(14)*
Diagnostic radiation	Kaiser Permanente case-controlled	1.3–39	Bone marrow dose calculated and scaled	Boice et al., 1991 *(15)*
Thorotrast exposure	Denmark *cerebral arteriography incidence	4.6	Compared with general population	Anderson et al., 1992 *(16)*
MGUS Experiment in rhesus monkeys	animal	MGUS and MM seen in experimental animals	*Radiation therapy *Rescued with bone marrow transplant	Radl et al., 1991 *(17)*

MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.
[a]This is initial report of ongoing analysis; 36 myeloma cases among 1500 exposed individuals

of the subsequent development of MM. The thorotrast exposure in Denmark is a well-established example of a special circumstance that can lead to an unexpected risk—in this case, the risk being subsequent development of MM *(16)*.

Of particular interest and relevance is the study by Radl in rhesus monkeys *(17)* in which a special technique was used that involved administering radiation to the animals then "rescuing" them by means of bone marrow transplantation. Such animal studies indicate that both MGUS and myeloma can result from high-level ionizing radiation exposure.

Overall, there is little doubt that exposure to ionizing radiation, particularly when exposure is directly to bone marrow sites, can lead to MM *(4,5)*. The risk is dose- and time-dependent. This observation, plus related observations correlating an increased likelihood of several cancers, supports the need for continued protection against potential radiation exposure. Individuals at risk must be informed and appropriate protections put in place.

4. OCCUPATIONAL EXPOSURES TO CHEMICALS AND MANUFACTURED MATERIALS AND THE RISK FOR MM

Although most now agree that radiation exposure can cause MM in particular circumstances, the risk of MM, MGUS, or both following exposure to chemicals remains controversial *(4,5)*. The challenge is to assess exposure to carcinogenic chemicals in patients developing MM and related disorders. The diversity and complexity of potential exposures *(18)* among various occupations and the subsequent correlation of such exposures with the development of a rather rare malignancy such as myeloma is a major epidemiologic challenge. It is to be expected that some results will be inconsistent. The occurrence of unintentional confounding factors and biases further complicates the situation *(9)*. Nonetheless, consistent patterns have been observed (Table 4), as well as several strong associations that provide "proof of principle" that chemical exposures can cause MM.

4.1. Pesticides

The largest number of studies of chemical exposure involves pesticides and agents used in farming occupations *(19–36)*. In 10 out of 14 studies of pesticide exposures, a substantial increase in the risk of MM was seen, with risk ratios in the range of 3.2 to 8.2 (*see* Tables 4 and 5). Of particular interest is an increased risk associated with pesticide exposure combined with exposure to other toxic chemicals, which may occur during farming. Examples of these "added risk" exposures include paints and solvents, wood treatment chemicals, and diesel engine fumes, as well as potential infections transmitted from farm animals. The risk ratio can rise from 2.1 to 7.9 with such combination exposures. This compounding of risk is a recurring theme in analyses of studies of myeloma, i.e., there is a consistent pattern or increased risk for MM with higher exposure or combined exposures.

Table 4
Occupational Exposures to Chemicals and Manufactured Materials and Risk for Multiple Myeloma

Exposure	*Risk Ratio*	*Comments*
Pesticides	3.2–8.2	Overall: 10/14 studies positive
Pesticides alone	2.1	
Pesticides plus "farming"[a]	7.9	Other risk factors considered (e.g., paint, solvents, wood treatment chemicals, engine fumes, and infections)
Paints and solvents	1.7–5.5	Overall: 6/8 positive studies
All exposures	5.5	
"High" exposures[b]	10.0	Several studies indicate effects by dose and duration of exposure
Photographic chemicals	6.1	Single study, but supported by other data
Asbestos	1.7–61	Overall: 5/9 studies positive
"Benzene" plus petroleum refining	2.2–4.1	3/14 studies positive. Correlations complex (*see* text for discussion)
Weak associations:		
Hair-coloring products	1.4–4.39	• 4/7 studies positive • 4.39 risk ratio for black dyes
Miscellaneous exposures and occupations including, for example, Engine exhaust; metals (e.g., arsenic, lead); rubber and plastics industries; wood industries (esp. forestry); textile industries (incl wool spinners/weavers)	1.5–3.0	• Variable results mostly requiring further studies
Negative studies		
Alcohol	• Four negative studies	
Tobacco	• Nine negative studies	
	• One positive study (in Seventh Day Adventists)	Confounding factor(s) suspected (*see* text for discussion)

[a]"Farming" means added risks that occur while working on a farm.
[b]*See* ref. *38*.

4.2. Paints and Solvents

The trend of increased risk with combined exposures is also noted in eight studies of myeloma risk with exposure to paints and solvents in various occupations *(4,5,37–42)*. The risk ratio range is from 5.5 to 10 in individuals with average to high exposure to various components of paints and solvents. Six out of eight positive studies indicate the impact of both dose and duration of exposure.

Table 5
Epidemiologic Studies of Multiple Myeloma Among Farmers

Author (19–35)	*Location*	*Relative Risk*	*95% CI*	*Comments*
Boffetta	United States	3.4	(1.5–7.5)	
Cantor	Wisconsin	1.4	(1.0–1.8)	
Tollerud	North Carolina	0.06	NA	
Gallagher	Vancouver	2.2	(1.2–4.0)	
Nandakumar	Australia	1.4	(0.8–2.5)	
Steineck	Sweden	1.2	(1.1–1.3)	
Pearce	New Zealand	2.2	(1.3–3.8)	Aged 20–64 yr
		1.2	(0.8–2.0)	Aged 65+ yr
Burmeister	Iowa	1.5	NA*	
Brownson	Missouri	1.0	0.4–2.3	
Milham	Oregon/Washington	1.8	NA*	
Giles	Tasmania	0.8	NA	Men
		1.7	NA	Women
La Vecchia	Italy	2.0	(1.1–3.5)	
Fasal	California	1.0	NA	Men
		1.0	NA	Women
Flodin	Sweden	1.9	(1.1–1.9)	Men and Women
McLaughlin	Sweden	1.2	NA*	
Cuzick	England/Wales	1.6	NA	Risk calculated from % in paper

Adapted from ref. *36*.

Studies of paints and solvents highlight several other potential confounding factors, including the fact that the composition of the toxic material has changed over the decades. For example, benzene has been excluded from many products over the years. Other precautions have resulted in variations in risk, including the occasional increase in risk for MM in various occupations.

4.3. Photographic Chemicals

A study of exposure to photographic chemicals, which revealed a risk ratio of 6.1 for subsequent myeloma, raised many of the issues addressed in the studies of paint and solvent exposure *(35)*. The components of photographic chemicals have changed over the years, as have the facilities and precautions used by professional and amateur photographers. Patients presenting with myeloma during the 1980s and 1990s who had been exposed to photographic chemicals 20 or 30 yr earlier were potentially exposed to products prior to exclusion of known carcinogens. Also, the general precautions and use of ventilated dark rooms by photographers has increased substantially over the years. This highlights a prob-

lem with follow-up studies that is frequently overlooked. After an initial observation (e.g., myeloma in photographers), follow-up studies may fail to show such high levels of association, in part because the chemical composition and protective measures changed following early observations.

4.4. Asbestos

The correlations between asbestos exposure and MM are particularly interesting, *(4,5)* with five out of nine published studies providing evidence of a significantly increased risk. Again, much of the data suggests that co-exposures may account for variations among analyses.

4.5. Benzene and Other Petrochemicals

The correlation of benzene exposure with the incidence of myeloma in petroleum refining industries has led to particularly controversial data and conclusions *(43)*. In several reports, investigators concluded that there is a correlation between benzene exposure and the risk for myeloma. In a recent comprehensive review, however, the authors concluded that although benzene and benzene related products can lead to leukemia, MDS, and related disorders, there is not enough evidence to establish an association with MM. A recent meta-analysis of case-controlled studies assessing the relationship between occupational chemical exposures (including benzene) and the risk for myeloma provided helpful information *(44)*. A major source of benzene exposure in the studies analyzed was engine exhaust, and a strong correlation was found between myeloma and engine exhaust exposure, but not with benzene exposure. The authors proposed that several harmful chemicals present in engine exhausts—e.g., benzopyrene, ethylene, toluene, xylene, formaldehyde, and suspended particulate material—are potential culprits in these various studies, rather than the benzene itself. This can partly explain the conflicting study results and conclusions. More detailed molecular analyses designed to identify correlations between chemical levels in body tissues with the direct assessment of DNA damage will be helpful *(9,45)*. Carefully studied cases of high-level benzene or petroleum product exposure in individuals who developed MM have been informative. For example, in a case involving a patient who developed a plasmacytoma in the jaw (followed by widespread myeloma), this occurred at the site of chronic exposure to a petrochemical-containing dental adhesive since childhood. Specific studies confirmed local absorption of that carcinogen through buccal mucosa.

4.6. Miscellaneous Chemical Associations

Borderline associations and negative studies should also be reviewed for less common exposure relationships (Table 4). Borderline associations can reflect the variability of exposure more than the danger of the chemicals or exposures involved. Four out of seven studies indicated a positive relationship between

exposure to hair-coloring products and an increased risk for MM *(46–51)*. This is particularly true for exposure to black dyes *(46)*. Obviously, exposure to hair-coloring products includes individuals working in hairdressing and related industries, as well as product consumers. Because exposure varies among individuals, more detailed studies of individual cases at a molecular and tissue level will be required to document specific characteristics of potential exposure and the subsequent development of plasma cell disorders. Other exposures that increase the risk for MM include engine exhaust (see above) and metals (e.g., arsenic and lead), and exposures in the rubber and plastics industries, wood industry (especially in forestry workers), and various textile industries *(4,42,52,53)*.

4.7. Alcohol and Tobacco

It is unlikely that alcohol or tobacco use contributes to the development for MM. One of 10 studies indicated a positive relationship for the use of tobacco in Seventh Day Adventists. However, this finding is in such contrast to those of the other nine studies that it is felt that some other confounding factor(s) may account for it *(54,55)*.

4.8. Summary: Chemical and Industrial Exposures

Multiple studies in a wide variety of settings now support the evidence of principle that exposure to carcinogenic chemicals results in an increased likelihood of MM. Genetic susceptibility impacts the risk of specific exposures. There are enough data to recommend reduced exposures to potentially carcinogenic chemicals.

5. INFLAMMATORY AND AUTOIMMUNE DISORDERS ASSOCIATED WITH MM AND MGUS

5.1. Rheumatoid Arthritis

There is a long-standing notion that immune stimulation is an important pathogenic factor in the evolution of MM. Numerous studies have investigated the relationship of a variety of inflammatory and autoimmune diseases and the likelihood of developing MM or MGUS. It has proved very difficult to adequately assess the information generated. Studies have involved a broad range of patient and control populations. Multiple questions have been asked as part of the same study. Nonetheless, a number of comments can be made identifying several potentially important associations (Table 6). Perhaps the most striking associations have been with rheumatoid arthritis *(56–59)*. Four cohort studies have highlighted a strong relationship with MM (RR range: 3.3–9.5). These values are obviously highly relevant, but have been counterbalanced by other population- and hospital-based studies, which failed to reveal any relationship. Since there

Table 6
Inflammatory and Autoimmune Disorders
Associated With Multiple Myeloma and MGUS

Risk Ratio Observed/Expected	*Condition*	*Study Findings*
Multiple Myeloma		**High Risk**
3.5		Rheumatoid arthritis • 4 cohort studies: • RR: 3.3, 5.0, 8.1 and 9.5 • Separate hospital- and population-based studies
2.5–<3.5		• History of allergies • Shingles • Pneumonia • BCG immunization • Eczema • RR 0.6–3.1 • RR 0.7–2.7 • RR 1.1–2.6 • RR 1.0–3.0 • Variable results
		Lower Risk Disorder
1.5–<2.5		Multiple conditions, including: • Pernicious anemia • Hypothyroidism • Hyperthyroidism • Diabetes mellitus • Chronic disk disease • Various infections, including • chronic bronchitis • osteomyelitis • pelvic infection • urinary tract infection • ear nose and throat infections • scarlet/rheumatic fever • hepatitis • Diphtheria vaccination
MGUS		• Leishmaniasis • Cytomegalovirus infection

are important pathogenetic relationships between rheumatoid arthritis and MM, it is particularly relevant that high levels of interleukin-6 are observed in both disease. Recent studies have highlighted the possible pathogenic relationship between plasma cell disorders and the infectious process in rheumatoid arthritis, which will be discussed later in this chapter. Identifying the common predisposition, triggering factor(s), or both will be helpful in clarifying the relationships reported thus far.

5.2. Other Inflammatory Conditions

Several other relationships have been noted that pose a slightly lower level for MM (RR range: 2.5–3.5) *(4,5)*. The disease categories include a history of allergies—particularly to drugs, but also to household products—eczema, prior bacillus Calmette-Guérin immunization, and a prior history of shingles or pneumonia. Again, the results are not entirely consistent with various risk ratios reported in different types of studies and different populations. Nonetheless, there is enough of a positive correlation that a pathogenic relationship should be suspected for a subset of patients. Of note, the interest in microbial infections as the cause of many malignancies is on the rise *(60)*.

The role of infection as a trigger for MM is particularly difficult to assess, because patients with myeloma have a reduced immune response and, therefore, are susceptible to infection. Does this mean that patients with MM develop infections of different sorts because the immune system is already compromised, or, conversely, are the various infections part of the initial triggering process? As highlighted under the list of conditions associated with a lower risk (RR range: 1.5–2.5), a broad range of infections have been identified in this category. The infections involve most of the major organ systems: ear, nose, and throat, lungs, bone, urinary tract, cardiac, pelvic organs, and liver. Positive findings in such a diversity of studies strengthens the likelihood of a true pathogenic involvement. Of note, MGUS has also been associated with infections, specifically, Leishmaniasis and cytomegalovirus infection *(61)*.

5.3. Classification of Factors Involved in the Pathogenesis of MM and MGUS

The five categories of factors involved in the pathogenesis of MM are summarized in Table 7. Although familial or predisposing factors correlate with the evolution of myeloma and related disorders, remarkably little is known about them *(62)*. It is known that there are substantial racial variations in the rate of toxin metabolism and HLA differences that influence susceptibility to viruses, as well as deviations in DNA repair capability and the level of response to immune triggers (i.e., cytokines and hormones). How these factors vary among patients with myeloma is almost completely unknown *(62–67)*. Without this

Table 7
Factors Involved in the Pathogenesis of Multiple Myeloma and MGUS

Familial/predisposing factors:	Variations in toxin metabolism
	• P450 system polymorphisms
	• glutathione *S*-synthetase polymorphisms
	HLA differences influencing
	• viral susceptibility
	• IFN-α
	• IFN-γ
	Susceptibility to DNA injury
	• radiation sensitivity
	• DNA repair
	Intrinsic cytokine/hormone response patterns
	• cytokines: IL-6, IL-4, IL-10
	• hormones: sex and pituitary
Residential/social factors	Local pesticide spraying/contamination
	Socioeconomic status
	• poor living conditions
	Recreational/hobby exposures
	• garden chemicals
	Personal habit risk factors
	• hair dyes
Occupational exposures	Variations in toxin metabolism:
	• P450 system polymorphisms
	• glutathione *S*-synthetase polymorphisms
	HLA differences: influence susceptibility to
	• viral infection
	• IFN-α
	• IFN-γ
	Susceptibility to DNA injury
	• radiation sensitivity
	• DNA repair mechanisms
	Radiation
	• Chemicals, metals, other
Antigenic challenges	Infections
	Allergies
Inflammatory disease	
Autoimmune disease	
Stress factors	Tissue stress/injury from implants, fractures, trauma
Psychological stress	Secondary neuroendocrine/immune effects of psychological stress

HLA, human lymphocyte antigen; IL, interleukin; IFN, interferon.

information, it will be impossible to move forward with molecular epidemiology to identify specific factors that are causally linked to myeloma. The residential, occupational, recreational, and stress factors identified also vary from patient to patient.

The potential complexity at the level of the individual patient is astounding. How can one assess an individual with a complex family and exposure history? Consider, for example, a patient who experienced all of the following prior to the onset of MM: a well-documented family history of hematologic cancer; lived in a farming community where pesticide spraying was common; regular use of black hair dye; infectious mononucleosis as child and hepatitis C as an adult; experienced a broken leg in a skiing accident that required the insertion of a pin; psychological stress when a child died tragically in an automobile accident. The existence of such a multitude of risks in a single individual creates a daunting analytical problem.

In an effort to clarify and assess such patients, this author has analyzed demographic data since 1992, both in clinical practice at the Cedars-Sinai Comprehensive Cancer Center as well as through demographic questionnaires supplied to all myeloma patients who become members of the International Myeloma Foundation (IMF). This has resulted in a database of more than 1500 personal patients and more than 50,000 patient IMF members. Controlled data analysis is clearly a challenge (Table 8). First of all, it involves a relatively rare cancer for which multiple predisposing factors exist. Multiple exposures may have occurred with varying patterns of timing, dose, and duration in different residential and occupational settings. Basic parameters may be confounded by additional cofactors as basic as socioeconomic status, alcohol intake, and tobacco use.

Some possible solutions to this dilemma are listed in Table 9 *(6,8)*. The overriding assessment to be accepted is that multiple factors can be involved in a multistep process. Ideally, a small number of patients can be studied in great detail to assess the genetic predisposition and tissue sampling, as well as to obtain a detailed exposure history and provide follow-up. With such information available as a baseline, well-defined populations can then be studied in more detail, e.g., in terms of specific places of residence, occupations, and hobbies. Larger databases (e.g., those now available to the IMF) can be used to evaluate the initial observations more critically and ask highly focused questions (e.g., to determine the impact of a family history of myeloma, cancer, or both). It is obviously important to take advantage of ethnic, gender, and age differences in all planned registry, cohort, or population studies *(69,70)*.

6. GEOGRAPHIC CLUSTERS OF MM

One method of assessing risk factors for MM is to investigate clusters of myeloma. Although epidemiologists tend to roll their eyes at the mere mention

Table 8
Difficulties in Identifying Causal Factors for Myeloma and MGUS

Relatively rare diseases	Difficult to obtain meaningful statistics
Multiple predisposing factors	Family history Sex Race Age
Multiple toxic/trigger exposures involved (*see* Fig. 1)	Toxin Antigenic trigger Stressor
Timing, "dosing," duration of exposures critical	Level of intrinsic susceptibility Level of combined cellular impact
Similar exposures achieved in many different residences, occupations, hobbies, and infections/stressor	
Multiple potential confounders/biases	

Table 9
Solutions to Causal Analysis for Multiple Myeloma and MGUS

- Use multfactorial/multistep process as model
- Study patients on case-by-case basis, especially small (e.g., family) groups. This allows:
  - Genetic analysis e.g., P450, glutathione *S*-synthetase, DNA adducts
  - Tissue sampling
  - Detailed exposure history
  - Careful follow-up
- Focus on defined populations by
  - Residence: e.g., associated with dioxins
  - Occupation: e.g., high-risk occupations such as firefighters
  - Hobbies: e.g., use of toxic chemicals
- Use large databases to confirm initial observations
- Take advantage of ethnic, gender, age differences to study mechanisms

of "clusters," clusters do occur. Thus far, eight carefully studied myeloma clusters have been published in the medical literature (Table 10). Obviously, the methodology for studying clusters is difficult. In his analysis of the published data, Schwartz used a variety of techniques to correlate the reported clusters with exposure to environmental dioxins *(71–76)*. He noted, for example, that the reported clusters are consistently close to bodies of water or rivers. Using a unique statistical method, Schwartz was able to show that the eight clusters were more likely than not to be located adjacent to bodies of water (i.e., lakes, rivers, or seas) rather than in random geographic locations. Additionally, he was able to

Table 10
Reported Geographic Clusters of Multiple Myeloma

Location	*Year*	*Number of patients*	*Comments*
Thief River Falls	1970	7	Crude incidence: 10.6/100,000 No explanation
Aberdeen Scotland	1973	153	Evaluated NE Scotland 1960–1969 Crude incidence: 3.8 (vs 1.8)
Western Ireland	1985	117 MM 296 MGUS	Crude incidence: 4.5 (vs 1.1) High, but ? comparison
Petersburg Virginia	1979	21	Crude incidence: 11–12.5/100,000
Walney Island, UK	1992	7	Population: 11,000; therefore crude incidence very high
Baglan Bay, Wales	1992	42	42 myeloma deaths vs 28.3 expected
T Town, Japan	1991	7	Age-adjusted incidence: 7.3/100,000
Okechobee, Florida	1997	37	Age-adjusted incidence: 7.9/100,000

Data from ref. *72*.

show that dioxin exposure was more likely to occur near water and was associated with an increased risk for MM. Examples used for this analysis included the increased incidence of myeloma in fisherman eating dioxin-contaminated fish on a regular basis in several locations around the world, including Alaska, the Baltic Sea, waters around the United Kingdom, and Lake Okeechobee, Florida. Further support comes from studies of individuals exposed to high levels of dioxins secondary to the industrial explosion in Seveso, Italy, as well as the increased incidence in myeloma in obese patients (owing to the accumulation of dioxins in fatty tissue). All of the gathered data support the hypothesis that dioxin exposure significantly increases the risk for myeloma.

These cluster analyses provide enough background information to recommend more detailed analyses in the future. New techniques for analyzing clusters have been developed which show great promise for statistical robustness in classifying and evaluating clusters *(77)*.

7. THE INFORMATION GAP: PROBLEMS ABOUT SOURCES OF DATA ON TOXIC EXPOSURE

The preceding comments are based on data published in standard biomedical publications, including materials developed by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), the most respected source of information on carcinogenic risk. The IARC updates data (e.g., on dioxins) regularly *(78)* and susceptibility *(79)*. However, even the IARC has been subject to criticism for failing to classify known human carcinogens appro-

priately because of the possibility of industry backlash *(80)*. Researcher Lorenzo Tomatis was recently banned from setting foot in the IARC building in Lyon, France, because he accused the IARC of "soft-pedaling the risks of industrial chemicals." A new director was appointed in 2003.

Even more troubling is the lack of access to industrial or corporate medical data. Because toxic exposure can represent a source of potential litigation, much critical information exists in court documents and sealed corporate files. A recent book published by the The Center for Public Integrity highlights this issue and addresses the financial and geopolitical problems involved *(81)*. *Living Down Stream*, *(82)* by an ecologist, addresses the relationship between cancer and the environment, as well as public health concerns that arise because all information relevant to public safety and policy is not integrated for the common good.

Therefore, it is important to keep an open mind. Maybe "scientific" data and reviews do not always provide the full picture *(43)*. Vigilant, detailed, ongoing research is required to assess the nuances of relationships among chemicals and other toxins, the environment, and the risk for MM and other types of cancer. Does the metabolism of chemicals in the soil *(75)* pose a new unexpected risk? Are there occupations that unexpectedly confer an excessive risk for myeloma (e.g., elementary school teaching) *(83)*? Is there a possibility of myeloma clusters developing in Silicon Valley as a result of exposure to exotic chemicals in the computer industry or some other unexplained environmental hazard? *(84,85)* Are breast implants a new risk factor for myeloma and MGUS? A recent large case-control study shows that patients with MM are more likely to have breast implants *(85a)*. Why does Nogales, Arizona have 5 to 10 times the expected incidence of MM? Is it related to toxic dumping *(85)* and the water supply *(86)*? Only further studies will answer these and many more questions.

7.1. Viruses and MM and MGUS

As already discussed, many types of infection have been linked to myeloma. Viruses such as herpes zoster, bacterial infections such as pneumococcal pneumonia, plus other infections such as Leishmaniasis and syphilis have all been linked to the evolution of plasma cell disorders. Microbial infection has been linked to cancer overall *(60)*. Recently, questions were posed concerning whether infection plays a role beyond that of triggering the expansion of the abnormal clone via cytokine and other related mechanisms. Is myeloma the result of an aberrant idiotypic response to a specific infection or several types of infection? It has been demonstrated that the specificity of myeloma protein in patients with acquired immunodeficiency syndrome (AIDS) is against the gag protein region of the human immunodeficiency virus envelope *(86)*. Several reports have linked monoclonal gammopathies with hepatitis C infections *(87)*.

The increased incidence of myeloma in AIDS underscores the potential role of viruses in the pathogenesis of myeloma *(88)*. However, major reactivation of

interest in this area stemmed from the observation that Kaposi's sarcoma (KS) virus HHV-8 is present in the bone marrow of patients with MM and MGUS *(89,90)*. HHV-8 does not occur in myeloma cells but rather in accessory cells, e.g., dendritic and other such cells in the bone marrow. The initial observation of the KS virus in bone marrow led to a series of attempts by groups around the world to document the frequency with which HHV-8 appears in bone marrow and other tissue samples, as well as the level of HHV-8 antibody response in serum *(90)*. Conflicting results have been obtained. Several groups confirmed the presence of HHV-8 in MM bone marrow specimens using polymerase chain reaction (PCR), whereas others failed to do so using a variety of techniques. The search for serum antibodies to HHV-8 has been largely negative results. Explanations for this have included the generally immunosuppressed state of patients with myeloma, as well as the possibility of genetic heterogeneity in the HHV-8 involved in plasma cell disorders. A recent report documenting the molecular heterogeneity of HHV-8 supports the notion that a mutation of HHV-8 that does not trigger a strong antibody response may be involved *(91)*. Further studies are necessary to clarify the role of HHV-8 in MM.

Another series of studies indicated a possible role for the simian virus 40 (SV-40) or related viruses capable of producing SV-40 T-antigen in patients with MM *(93–96)*. In a study of patients with active myeloma, RNA found in the plasma of 89% of patients experiencing a relapse was studied by PCR and found to contain RNA with SV-40 T-antigen-binding sites. This raises the possibility that the SV-40 (or Epstein-Barr virus, various adenoviruses, human papilloma virus, and other viruses containing antigens with similar binding potential) may have a role in the pathogenesis of the active disease. Additional studies have measured the amount of the RNA with SV-40 T-antigen specificity. Initial results indicate that blood obtained from patients with active myeloma contains substantial RNA levels, as well as microvesicles evident on electron microscopy and can produce an in vitro a cytopathologic effect characteristic of that of the "stealth virus" (truncated cytomegalovirus). Further investigations are necessary to clarify the implications of these observations.

In summary, recent observations of viruses point to a strong likelihood that viral triggers may in some fashion be one of the multiple factors involved in the causation of MM.

8. THE POTENTIAL FOR PREVENTION OF MM AND MGUS

The accumulated data strongly support the notion that various types of environmental exposures—including chemicals, radiation, and viruses—significantly increase the risk for MM and related plasma cell disorders. The remarkable diversity of exposures makes prevention planning a challenging prospect. It is rather easy to suggest that prevention strategies designed to reduce toxic expo-

sures of known carcinogenic risk will help reduce the future incidence of myeloma. Many of the exposures discussed above are clearly carcinogenic. Appropriate precautions are only judicious at this point, not just for myeloma, but in general, because many individuals at risk for myeloma have already been exposed. What can be done for them? A recent report illustrating that Olestra can dramatically accentuate the excretion of dioxins highlights the possibility that high-risk individuals can be screened and receive short-term treatment to remove toxins that are present at elevated levels *(97)*. If DNA injury has already occurred, appropriate steps can be taken to reduce any potential for additional DNA injury or trigger factors such as a viral infection and local or systemic stressors. The more we learn, the better we can reduce the incidence of myeloma, which remains difficult to treat and is as yet impossible to cure.

REFERENCES

1. Warburton P, Josua DE, Gibson J, Brown RD. CD10-(Calla)-positive lymphocytes in myeloma: evidence that they are a malignant precursor population and are of germinal centre origin. Leuk Lymphoma 1989; 1:11–12.
2. Harris CC, Hollstein M. Clinical implications of the p53 tumor-suppressor gene. N Engl J Med 1992; 329:1318–1326.
3. Potter M. The developmental history of neoplastic plasma cell in mice. Sem Haematol 1973; 10:19–31.
4. Herrington LJ, Weiss NS, Olshan AD: Multiple myeloma. In: Schottenfeld D, Fraumerni JF Jr, eds. Cancer Epidemiology and Prevention. 2nd ed. New York, NY: Oxford University Press; 1996:946–970.
5. Riedel DA, Pottern LM. The epidemiology of multiple myeloma. Hematol Oncol Clin N Am 1992; 6:225–247.
6. Schwartz J. Multinational trends in multiple myeloma. Annals NY Acad Sci 1990; 63:215–244.
7. Davis DL, Hoel D, Fox J, Lopez A. International trends in cancer mortality in France, West Germany, Italy, Japan, England and Wales, and the USA. Lancet 1990; 336:474–481.
8. Miller BA, Ries LAG, Hankey BF, et al. 1993 SEER Cancer Statistics: Review. 1973–1990. National Cancer Institute; NIH Publication No. 93-2789, Washington, DC.
9. Taubes G. Epidemiology faces its limits. Science 1999; 269:164–169.
10. Shimizu Y, Kato II, Schull WJ. Studies of the mortality of A-bomb survivors: 1950–1985. Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 1990; 121:120–141.
11. Rabbitt-Roff S. Incidence of multiple myeloma in UK veterans exposed to atomic radiation in Pacific Nuclear tests. Occup and Environ Med 2003; 60:e18–e36.
12. US Department of Energy (DOE) Web site: http://www.hanford.go~safety/myelomaindex/htm. Posted 02/05/98.
13. Gilbert ES, Fry SA, Wigs LD, Voelz GL, Cragle DL, Petersen GR. Analyses of combined mortality data on workers at the Hanford site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. Radiat Res 1989; 120:19–35.
14. Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. BMJ 1986; 293:845–854.
15. Boice JD, Morin MM, Glass AG, et al. Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. JAMA 1991; 265:1290–1294.
16. Andersson M, Sotrm HH. Cancer incidence among Danish Thorotrast-exposed patients. J Natl Cancer Inst 1992; 84:1318–1325.

17. Radl J, Liu M, Hoogeveen CM, et al. Monoclonal gammopathies in long-term surviving Rhesus monkeys after lethal irradiation and bone marrow transplantation. Clin Immunol Immunopathol 1991; 60:305–309.
18. Arcos J, Argus M, Woo Y, eds. Chemical Induction of Cancer Modulation and Combination Effects: An Inventory of the Many Factors Which Influence Carcinogenesis. Boston, Mass: Birkhauser; 1995.
19. Boffetta P, Stellman SD, Garfinkel L. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer 1989; 43:554–559.
20. Cantor KP, Blair A. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. J Natl Cancer Inst 1984; 72:251–255.
21. Tollerud DJ, Brinton LA, Stone BJ, Tobacman JK, Blattner WA. Mortality from multiple myeloma among North Carolina furniture workers. J Natl Cancer Inst 1985; 74:799–801.
22. Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH. Allergies and agricultural exposure as risk factors for multiple myeloma. Br J Cancer 1983; 48:853–857.
23. Nandakumar A, English DR, Dougan LE, Armstrong BK. Incidence and outcome of multiple myeloma in Western Australia, 1960 to 1984. Aust N Z Med 1988; 18:774–779.
24. Steineck G, Wiklund K. Multiple myeloma in Swedish agricultural workers. Int J Epidemiol 1986; 15:321–325.
25. Pearce NE, Smith AH, Fisher DO. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. Am J Epidemiol 1985; 121:225–237.
26. Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA. Case-control study of multiple myeloma and farming. Br J Cancer 1986; 54:493–500.
27. Burmeister LF. Cancer in Iowa farmers: recent results. Am J Ind Med 1990; 18:295–301.
28. Brownson RC, Reif JS, Chang JC, Davis JR. Cancer risks among Missouri farmers. Cancer 1989; 64:2381–2386.
29. Milham S. Leukemia and multiple myeloma in farmers. Am J Epidemiol 1971; 94:307–310.
30. Giles GG, Lickiss JN, Baikle MJ, et al. Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972-1980: occupational and familial aspects. JNCI 1984; 72:1233–1240.
31. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Occupation and lymphoid neoplasms. Br J Cancer 1989; 60:385–388.
32. Fasal E, Jackson EW, Klauber MR. Leukemia and lymphoma mortality and farm residence. Am J Epidemiol 1968; 87:267–274.
33. Flodin U, Fredriksson M, Persson B. Multiple myeloma and engine exhausts, fresh wood, and creosote: a case-reference study. Am J Ind Med 1987; 12:519–529.
34. McLaughlin JK, Linet MS, Stone BJ, et al. Multiple myeloma and occupation in Sweden. Arch Environ Health 1988; 43:7–10.
35. Cuzick J, De Stavola B. Multiple myeloma: a case-control study. Br J Cancer 1988; 57:516–520.
36. Blair A, Zahm SH. Cancer among farmers. Occupational Med 1991; 3:335–354.
37. Bethwaite PB, Pearce N, Fraser J. Cancer risks in painters: study based on the New Zealand cancer registry. Br J Ind 1990; 47:742–746.
38. Lundberg L. Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand J Work Environ Health 1986; 12:108–113.
39. Demers PA, Vaughan TL, Koepsell TD, et al. A case-control study of multiple myeloma and occupation. Am J Ind Med 1992; 23:629–639.
40. Friedman GD. Multiple myeloma: relation to propoxyphene and other drugs, radiation and occupation. Int J Epidemiol 1986; 15:423–425.
41. Pottern LM, Heineman EF, Olsen JH, Raffn E, Blair A. Multiple myeloma among Danish women: employment history and workplace exposure. Cancer Causes Control 1992; 3:427–432.
42. Heineman EF, Olsen JH, Pottern LM, Gomez M, Raffn E, Blair A. Occupational risk factors for multiple myeloma among Danish men. Cancer Causes Control 1992; 3:555–568.

43. Bergsagel DE, Wong O, Bergsagel PL, et al. Benzene and multiple myeloma: appraisal of the scientific evidence. Blood 1999; 94:1174–1182.
44. Sonada T, Nagata Y, Mori M, Ishida T, Imai, K. Meta-analysis of multiple myeloma and benzene exposure. J Epidemiol 2001; 11:249–254.
45. Ambrosone CB, Kadlubar FF. Toward an integrated approach to molecular epidemiology. Am J Epidemiol 1997; 146:912–918.
46. Thun MJ, Altekruse SF, Namboodiri MM, Calle EE, Myers DG, Heath CW Jr. Hair dye use and risk of fatal cancers in US women. J Natl Cancer Inst 1994; 86:210–215.
47. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Blair A. Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia. Am J Public Health 1992; 82:990–997.
48. Herrington LJ, Weiss NS, Koepseli TD, et al. Exposure to hair-coloring products in relation to the risk of multiple myeloma. Am J Public Health 1994; 84:1142–1144.
49. Brown LM, Everett GD, Burmfister LF, Blair A. Hair dye use and multiple myeloma in white men. Am J Public Health 1992; 82:1673–1674.
50. Teta JM, Walrath J, Meigs JW, Flannery JT. Cancer incidence among cosmetologists. J Natl Cancer Inst 1984; 72:1051–1057.
51. Eriksson M, Karisson M. Occupational and other environmental factors and multiple myeloma: a population-based case-control study. Br J Ind Med 1992; 49:95–103.
52. Hansen ES. A follow-up study on the mortality of truck drivers. Am J Ind Med 1993; 23:811–821.
53. Kawachi I, Pearce N, Fraser J. A New Zealand cancer registry-based study of cancer in wood workers. Cancer 1989; 64:2609–2613.
54. Linet MS, McLaughlin JK, Hsing AW, et al. Is cigarette smoking a risk factor for non-Hodgkin's lymphoma or multiple myeloma? Results from the Lutheran Brotherhood Cohort Study. Leuk Res 1992; 16:621–624.
55. Mills PK, Newell GR, Beeson WL, Fraser GE, Phillips RLP. History of cigarette smoking and risk of leukemia and myeloma: results form the Adventists Health Study. J Natl Cancer Inst 1990; 82:1832–1836.
56. Isomarki HA, Hakulinen U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chron Dis 1978; 31:691–696.
57. Katusic S, Beard CM, Kurland L, Weis JW, Bergstralh E. Occurrence of malignant neoplasm in the Rochester, Minnesota, rheumatoid arthritis cohort. Am J Med 1985; 78 (suppl 1A):50–55.
58. Matteson EL, Hickey AR, Maguire L, Tilson JJ. Urowitz MB. Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD registry. Rheumatoid Arthritis Azathioprine Registry Steering Committee. J Rheumatol 1991; 18:809–814.
59. Eriksson M. Rheumatoid arthritis as a risk factor for multiple myeloma: a case-control study. Eur J Cancer 1993; 29A:259–263.
60. J Parsonnet, ed. Microbes and Malignancy: Infection as a Cause of Human Cancers. New York, NY: Oxford University Press; 1999.
61. Haas H, Anders S, Bornkamm, GW, et al. Do infections induce monoclonal immunoglobulin components? Clin Exper Immunol 1990; 81:435–440.
62. Brown L, Linet M, Greenberg R, et al. Multiple myeloma and family history of cancer among blacks and whites in the US. 1999; 85:2385–2390 Cancer (Am Ca Soc).
63. Santella R. Immunological methods for detection of carcinogens: DNA damage in humans. Cancer Epidemiology, Biomarkers & Prevention 1999; 8:733–739.
64. Perera FP. Environment and cancer: who is susceptible? Science 1997; 278:1068–1073.
65. Chen S, Liu Q, Piu C, et al. Higher frequency of glutathione S-transferase deletions in black children with acute lymphoblastic leukemia. Blood 1997; 89:1701–1707.
66. Spencer D, Masten S, Lanier K, et al. Quantitative analysis of constitutive and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced cytochrome P450 1B1 expression in human lymphocytes. Cancer Epidemiology, Biomarkers & Prevention 1999; 8:139–146.

67. Roberts S, Spreadborough A, Bulman B, Barber J, Evans D, Scott D. Heritability of cellular radiosensitivity: a marker of low-penetrance predisposition genes in breast cancer? Am J Hum Genet 1999; 65:784–794.
68. I dos Santos Silva, ed. Cancer epidemiology: principles and methods. International Agency for Research on Cancer, World Health Organization; 1999; Lyon, France, Oxford University Press.
69. Miller BA, Bolonel LN, Bernstein L, et al, eds. Racial/Ethnic Patterns of Cancer in the United States: 1988-1992. Bethesda, Md: National Cancer Institute; 1996. NIH Pub. No. 96-4104.
70. Tajima K, Sonoda S, eds. Ethnoepidemiology of Cancer. Tokyo, Japan: Japan Scientific Societies Press; 1996.
71. Huff J, Lucier G, Tritscher A. Carcinogenicity of TCDD: experimental, mechanistic, and epidemiologic evidence. Ann Rev Pharmacol Toxicol 1999; 34:343–372.
72. Schwartz G. Multiple myeloma: clusters, clues, and dioxins. Cancer Epidemiology, Biomarkers & Prevention 1997; 6:49–56.
73. Bertazzi P, Pesatori A, Bernucci I, Landi M, Consonni D. Dioxin exposure and human leukemias and lymphomas: lessons from the Seveso accident and studies on industrial workers. Leukemia 1999; 13 (suppl 1):S72–S74.
74. Cranor CF, Davis D, Defur PL, et al. Brief Amici Curiae of the Lymphoma Foundation of America. The Supreme Court of the United States. No. 02-271: Dow Chemical Company, Monsanto Company, et al v Daniel Raymond Stephenson, Susan Stephenson, Daniel Anthony Stephenson, Emily Elizabeth Stephenson, Joe Isaacson, and Phyllis Lisa Isaacson. Counsel Press, 2003.
75. Lewis D, Garrison A, Wommack K, Whittemore A, Steudler P, Melillo J. Influence of environmental changes on degradation of chiral pollutants in soils. Nature 1999; 401:898–901.
76. Davis D, Magee B. Cancer and industrial chemical production. Science 1979; 206: 1356–1357.
77. Methods for investigating localized clustering of disease. In: Alexander FE, Boyle P, eds. IARC Scientific Publications No. 135. Lyon, France: Oxford University Press; 1996.
78. Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 69. Lyon, France: Oxford University Press; 1997.
79. Vineis P, Malat N, Lang M, et al, eds. IARC Metabolic Polymorphisms and Susceptibility to Cancer. Lyon, France. Oxford University Press. Publication Number 148, 1999.
80. Ferber D. Carcinogens: IARC, lashed by critics, WHO's cancer agency begins a new regime. Science 2003; 301:36–37.
81. Fagin D, Lavelle M, and the Center for Public Integrity. Toxic Deception: How the Chemical Industry Manipulates Science, Bends the Law and Endangers Your Health. 2nd ed. Monroe, Me: Common Courage Press; 1999.
82. Steingraber S. Living Downstream: An Ecologist Looks at Cancer and the Environment. Reading, Mass: Addison-Wesley Publishing Company, Inc; 1997.
83. Figgs LW, Doscemeci M, Blair A. Risk of multiple myeloma by occupation and industry among men and women: a 24-state death certificate study. J Occup Med 1994; 36:1210–1221.
84. Herbert B. "Sick and suspicious." The New York Times. September 4, 2003, p. A25.
85. Herbert B. "Clouds in Silicon Valley." The New York Times. September 8th 2003, p. A24.
85a. Vescio RA, Hamilton AS, Silverman SL, Berenson JR. Breast implant exposure is more prevalent in women with multiple myeloma: a case-control study. Blood 2002; 100:11:605a.
86. Price R. Nogales: something is very wrong. USA Today. October 27, 1993.
87. Sanchez R. Water quality problems in Nogales, Sonora. Tijuana, Mexico: Department of Urban and Environmental Studies, El Colegio De La Frontera Norte; 1995, p. 2.
88. Konrad R, Kricka L, Goodman DBP, Goldman J, Silberstein L. Myeloma-associated paraprotein directed against the HIV-1 p24 antigen in an HIV-1 seropositive patient. N Eng J Med 1993; 328:1817–1820.

89. Beld M, Penning M, van Putten M, et al. Low levels of hepatitis C virus RNA in serum, plasma, and peripheral blood mononuclear cells of injecting drug users during long antibody-undetectable periods before seroconversion. Blood 1999; 94:1183–1191.
90. Goedert J, Coete T, Virgo P, et al, for the AIDS-Cancer Match Study Group. Spectrum of AIDS-associated malignant disorders. Lancet 1998; 351:1833–1839.
91. Retting MB, Ha HJ, Vescio RA, et al. Kaposi's sarcoma-associated herpes virus infection of bone marrow dendritic cells from multiple myeloma patients. Science 1997; 276: 1851–1854.
92. Jarrett R. Prevalence of human herpesvirus 8 in multiple myeloma patients [abstract]. Multiple Myeloma Workshop; September 1999; p 83. Abstract 154.
93. Taret K, Chang Y, Klein B. KSHV is not causally associated with multiple myeloma [abstract]. Multiple Myeloma Workshop; September 1999; p 84. Abstract 155.
93a. Yi Q, Ekman M, Anton SD, et al. Blood dendritic cells from myeloma patients are not infected with Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) [abstract]. Multiple Myeloma Workshop; September 1999; p 85. Abstract 156.
94. Wiemer E, Van Suest P, Segever CM, Sonneveld, P. Detection of Kaposis' sarcoma-associated herpesvirus in mononuclear blood cells of patients with multiple myeloma [abstract]. Multiple Myeloma Workshop; September 1999; p 86. Abstract 157.
95. Gao S, Zhang Y, Deng J, Rabkin C, Flore O, Jensen H. Molecular polymorphism of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) latent nuclear antigen: evidence for a large repertoire of viral genotypes and dual infection with different viral genotype. J Infect Dis 1999; 180:1466–1476.
96. Durie B, Urnovitz J. Cell and molecular biology of simian virus 40: implications for human infections and disease. J Natl Cancer Inst 1999; 91:1166–1167.
97. Durie BGM, Urnovitz HB, Murphy WH. RNA in the plasma of multiple myeloma patients. Acta Oncologica 2000; 39:789–796.
98. Martin W. Melanoma growth stimulatory activity (MGSA/GRO-() chemokine genes incorporated into an African green monkey simian cytomegalovirus-derived stealth virus. Exp Mol Pathol 1999; 66:15–18.
99. Butel J, Arrington A, Wong C, Lednick J, Finegold M. Molecular evidence of simian virus 40 infections in children. J Infect Dis 1999; 180:884–887.
100. Hahn W, Counter C, Lundberg A, Beijersbergen R, Brooks M Weinberg R. Creation of human tumor cells with defined genetic elements. Nature 1999; 400:464–472.
101. Geusau A, Tschachler E, Meixner M, et al. Olestra increases faecal excretion of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Lancet 1999; 354:1266–1267.