

Review

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Multiple Myeloma: Clusters, Clues, and Dioxins¹

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Abstract

Multiple myeloma (MM) is a B-cell neoplasm of unknown etiology. We searched for etiological clues by examining the literature on geographic clusters of MM. We searched the MEDLINE database from 1966 to 1996 for spatial occurrences of MM that were significantly greater than expected (spatial "clusters"). Eight clusters with verified diagnoses of MM were identified. All of the eight clusters occurred in locations that were proximate to a body of water. Six of these bodies of water are known to have been contaminated with dioxins.

We hypothesize that the observed association between MM and proximity to bodies of water is caused by exposure to dioxins in individuals who consume local fish and seafood. This hypothesis is consistent with the significantly elevated risks for MM in groups with high consumption of dioxin-contaminated fish, e.g., Baltic Sea fishermen and Alaskan Indians, and among persons accidentally exposed to dioxins in Seveso, Italy. Dioxins are immunotoxic and inhibit the differentiation of B cells. Thus, dioxins are plausible myelomagens. A dioxin hypothesis could illuminate many epidemiological features of MM and may suggest new avenues for analytic research.

Introduction

MM³ is a hematological cancer characterized by the malignant proliferation of plasma cells and plasma cell precursors (immunoglobulin-producing cells of the B-cell lineage). It is the commonest clinical syndrome of a spectrum of disorders, the plasma cell dyscrasias or monoclonal gammopathies. Common to these disorders is the proliferation of a single clone of immunoglobulin-secreting cells and the resultant increase in serum levels of a single immunoglobulin (1).

MM accounts for approximately 14 of all malignancies in

the United States and affects Blacks twice as often as Whites. The annual age-adjusted (1970 U.S. standard) incidence rates for MM are 1.7 and 3.2 per 100,000 for White men and women (respectively) and 10.2 and 6.7 for Blacks. The racial difference in incidence rates does not appear to result from differences in socioeconomic factors (2).

The etiology of MM is obscure. Exposure to ionizing radiation is an established risk factor. However, because few people have significant exposure to ionizing radiation, most cases of MM must have other causes. Other risk factors for MM are less well established and include exposure to farming, pesticides, and petroleum products (3). Because MM is a disorder of proliferating immune cells, "chronic antigenic stimulation" has been proposed as an etiological factor (4, 5). However, the results of most investigations of that hypothesis have been negative (2, 3).

We recently investigated a cluster of MM that was located near a large body of water.⁴ Review of the literature revealed that several other clusters of MM have been reported; these also were located near bodies of water. The association between MM and bodies of water has not been widely recognized, however, and suggests a role for environmental pollutants. This suggestion is strengthened by the observation that many of these bodies of water have been contaminated with dioxins. The purposes of this paper are to: (a) review the literature on clusters of MM; (b) review the evidence of dioxin contamination of these bodies of water; and (c) develop the hypothesis that dioxins are a biologically plausible cause of MM. Before reviewing these clusters, we briefly review some toxicological properties of dioxins.

Dioxins. In general usage, the term "dioxin" refers to the members of three chemical classes with similar biological and toxicological effects. These are the PCDDs, PCDFs, and coplanar PCBs (6). Dioxins are ubiquitous environmental pollutants that are formed as by-products in many industrial activities that use chlorine. The best studied and most toxic of the dioxins is TCDD, a contaminant in the synthesis of 2,4,5-trichlorophenoxyacetic acid, an herbicide and defoliant (7, 8).

TCDD produces a variety of toxic effects in laboratory animals at very low doses. It is embryotoxic, teratogenic, and carcinogenic (9). The immune systems in animals are particularly sensitive to TCDD. Impairments in both T-cell- and B-cell-mediated immune functions occur at doses of TCDD that do not produce overt signs of general toxicity (10). Although TCDD is a known carcinogen in animals, the carcinogenic effects of TCDD in humans have been more difficult to evaluate. IARC has classified TCDD and occupational exposure to phenoxy acid herbicides as a possible human carcinogen (group 2B; Ref. 11).

Over 95% of human exposures to dioxins comes from food. Approximately 1% of dioxin exposure comes from breathing contaminated air, and a smaller amount comes from

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³ The abbreviations used are: MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; NHL, non-Hodgkin's lymphoma; PCB, polychlorinated biphenyl; PCDD, polychlorinated *p*-dioxin; PCDF, polychlorinated dibenzofuran; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; CI, confidence interval; RR, relative risk.

⁴ G. G. Schwartz, R. D. Rodriguez, P. Gomez, R. Duncan, and E. T. Trapido, unpublished data.

drinking contaminated water (6). Dioxins are lipophilic and accumulate in fatty tissue such as milk, meat, and fish. Contaminated fish and shellfish are an important source of dioxins in people with a diet high in fish (12). Sport-caught fish is the major source of dioxins for the general population (13) (14).

Materials and Methods

We searched the MEDLINE data base (in all languages) from January 1966 to January 1996 in an attempt to identify all spatial clusters of MM. We did not restrict the search to reports that used the word "cluster" in the title or abstract. Each cluster was examined for references to other clusters.

The definition of a spatial disease "cluster" and of a cluster's geographic boundaries is the subject of debate (15). We defined a "cluster" as a statistically significant excess of disease in a definable location. We accepted the geographic bounds of the clusters as those given by the authors of the individual reports. To be included, a cluster must have occurred within a defined geographic area, such as a city, county, or administrative district. We excluded clusters that lacked verification of MM, either via laboratory tests or death certificates.

We evaluated each cluster with respect to its proximity to a body of water. A cluster was considered "proximate" to a body of water if the geographic bounds of the location, as seen on our atlas (Today's World Ref. 16), included a coastline, river, or lake. For clusters within the continental U.S., proximity to bodies of water was evaluated using MapQuest (GeoSystems Global Corp.), an interactive atlas available on the Internet. This permitted resolution to a scale as large as 1 inch = 1.7 miles. We used MEDLINE to search for possible contamination of these bodies of water using the text words "water pollution," "fishes," "organochlorines," "PCBs," and "dioxins." Because carnivorous marine mammals are at the apex of the marine food pyramid, dioxin levels in these mammals, where available, were used as an indicator of marine pollution (17).

To evaluate bias in the selection of locations near water, we estimated an "expected" prevalence of proximity to bodies of water using "control" locations. Using the index of our atlas (16), we selected 50 control locations as follows. Two locations were randomly selected from each letter of the alphabet, A–Y. A table of random numbers was used to select control locations. A random number, r , indicated the r th location listed under the designated letter in the index. For example, under letter "A," the random number "10" indicated the 10th location, "Aba, Nigeria." Number "21" corresponded to "Abagner Qi, China." We repeated this procedure for each succeeding letter. We excluded locations with known clusters of MM and locations that were purely aquatic (e.g., the Pacific Ocean), as well as names indicating topographical features (e.g., Mt. Everest). Proximity to water in the control locations was evaluated using the same methods described above.

Results

Eleven clusters were identified using the criteria described above. Four were excluded: one due to lack of geographic information (18); two due to lack of disease verification (19, 20); and one because it was a preliminary report of a cluster that was published subsequently after longer follow-up (21). Thus, seven published clusters were available for review. We included our recent cluster, for a total of eight.

Geographic Clusters of MM and Dioxin Contamination

Thief River Falls, MN. The first reported cluster of MM occurred in Thief River Falls, MN (22). Thief River Falls (1970

population of 7151) is located 50 miles northeast of Grand Forks, ND. The Thief River Falls cluster came to attention when six cases of MM were diagnosed in the year 1968 (0.23 expected). When incidence rates were evaluated for the time period 1960 through 1968, the crude incidence rate remained elevated at 10.6 per 100,000 per year (3.0 expected, based on 7 cases). Of the seven cases, all were White; five were female. Two patients were husband and wife. None of the patients had a medical history of significant radiation exposure or unusual history of cancer. None shared a common association save for their residence in Thief River Falls. All patients lived in widely scattered locations throughout the town. The authors had no explanation for this cluster.

Dioxin Levels. Thief River Falls is proximate to the Thief and Red Lake Rivers. Historical data on dioxin levels were not available in these locations.

Aberdeen, Scotland. The second cluster was reported in 1973, when Dawson and Ogston drew attention to the high rates of "myelomatosis" in Northeast Scotland (23). ("Myelomatosis" includes MM and plasmacytoma, i.e., a solitary plasma cell tumor without evidence of disseminated disease.) The authors studied incidence and mortality from myelomatosis and usual place of residence for the period 1960–1969. Compared to the whole of Scotland, crude incidence and mortality rates were significantly higher in Aberdeen (3.4 versus 1.8 per 100,000 per year, incidence; 2.65 versus 1.67 per 100,000 per year, mortality). Eight % of the incident cases of myelomatosis (13 of 153) were plasmacytomas, and their geographic distribution paralleled the distribution of MM. There was no evidence of clustering of myelomatosis in time. The authors had no explanation for the elevated rates in Aberdeen.

Dioxin Levels. Aberdeen is a coastal city proximate to the Dee and Don Rivers and to the North Sea. Organochlorine residues were reported from prey seals (*Halichoerus grypus*), harp seals (*Phoca groenlandica*), and porpoises (*Phocaena phocaena*) taken from varying locations of Scotland's coastal waters. Pesticide contamination was greater in the seals and porpoises on the east coast of Scotland (taken from an area from Aberdeen to Tay estuary) than in specimens from the west and north coasts. Total residue concentrations of pesticides in seal blubber were as high as 73.3 ppm pesticides (dieldrin + total DDT; Ref. 24).

Western Ireland. In the third cluster, Greally *et al.* (25) noted an increased incidence of monoclonal gammopathy (the presence of a monoclonal protein in serum or urine) and MM in the West of Ireland. The incidence of monoclonal gammopathies was determined by examining laboratory records from hospitals that performed serum protein electrophoresis. Patients with monoclonal gammopathy were followed-up using hospital records. From January 1976 to August 1983, 196 cases of monoclonal gammopathy and 17 cases of MM were observed. The incidence of MM was highest in hospitals of the Western Health Board, serving Counties Galway, Mayo, and Roscommon. The crude incidence rate for MM in the Western Health Board was 1.5 per 100,000 per year, versus 1.1 per 100,000 per year for the South of Ireland (Counties Cork and Kerry). Although these rates were not age adjusted, the age structures of West and South Ireland populations reportedly do not differ. The authors speculated that the higher rate, for MM in West Ireland could be due to higher levels of background radiation. However, they acknowledged that studies of cancer mortality and background radiation levels in Ireland have been negative (26).

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Dioxin Levels. The west coast of Ireland borders the Atlantic Ocean. Organochlorine pesticide residues and PCBs were examined in 2 otters (*Lutra lutra*) from Ireland (27). Dieldrin, dichlorodiphenyldichloroethane (DDE), and PCBs were detected in all samples and were highest in otters from harbor areas. Elevated dioxin levels were observed in two of the three otters collected in an area corresponding to the Western Health District (total organochlorine levels of 109 mg/kg and 170 mg/kg). Levels of mercury, another common pollutant, were not elevated.

Petersburg, VA. The fourth cluster was described by Ende in Petersburg, Virginia (28). During 1971-1978, 21 cases of MM were diagnosed in the city of Petersburg. Fifteen of these occurred in a smaller zone of the city, termed the "target area," population 15,000-17,000. The crude incidence rate was calculated as 11-12.5 per 100,000 per year. The target area was predominantly Black. Of the 15 cases, 7 were Black males, 7 were Black females, and 1 was a White male. Ende reported that "an effort was made to see if there could be an association between multiple myeloma and Kepone, the chemical reported to have deleteriously affected workers recently in the nearby community of Hopewell, Virginia." Ende questioned seven MM patients in his care but found no association with Kepone (see below). He noted that four incident cases of MM were seen during 1971-1978 in the Hopewell Hospital.

Dioxin Levels. Petersburg is located in eastern Virginia proximate to the James and Hopewell Rivers, an area that was historically contaminated with the pesticide, Kepone. The history of the Kepone disaster has been comprehensively reviewed (29, 30). Briefly, Kepone (chlordecone) is a persistent polychlorinated hydrocarbon pesticide that is no longer manufactured in the U.S. From 1966-1974, 1.6 million pounds of Kepone were produced by Allied Chemical Corporation in its Hopewell, VA plants. The last operating plant was closed as a public health hazard in 1975 (31).

Kepone produces a range of acute toxicities in laboratory animals and is a carcinogen in rodents (32). Although the first cases of Kepone toxicity in humans were recognized in 1975, subsequent investigations revealed that marine life in the Tidewater region of Virginia had been contaminated with Kepone for a decade. Kepone from the Hopewell sewage treatment plant had contaminated local waterways. Air, water, and especially fish, were grossly contaminated. Kepone levels measured 0.3 ppb in the James River. These values were biomagnified in fish and shellfish. Thus, clams and oysters from the James River at locations 8-64 miles from Hopewell contained 0.2-0.8 parts per million (ppm) of Kepone; liver and entrails of bass and bream had concentrations up to 14 ppm. Concern about widespread human exposure through the consumption of contaminated seafood led to a government ban on taking shellfish and finfish from the James River.

Petersburg is located 8.2 miles southwest of the Kepone plant at Hopewell, VA. Although none of the patients interviewed by Ende had worked at the Kepone plant, they may have been exposed to Kepone unknowingly via the consumption of local fish and shellfish.

Island of Walney. The fifth MM cluster occurred on the Island of Walney (population 11,000), a strip of land separated by a narrow channel from the coastal town of Barrow in Furness, Cumbria, United Kingdom (33). Between 1974 and 1980, seven cases of MM were observed in Walney versus 2.8 expected ($P < 0.02$). An epidemiological investigation was undertaken in response to residents' concerns about the etiological role of

a nuclear reprocessing plant, located 15 miles up the coast at Sellafield.

A case-control study was performed in South Cumbria (the health district that includes Walney Island) using 34 cases of MM and 69 community controls. Cases and controls did not differ with respect to previous medical history, occupational exposures to radiation, or other suspected risk factors. However, the study uncovered one significant difference: cases had resided longer in the seaside town of Barrow in Furness. Forty-eight % of the cases versus 25% of the controls had lived in Barrow for more than 20 years ($P = 0.05$). The authors noted, "Barrow constitutes the Irish Sea coast of the district and almost all Barrow residences are within 10 kilometers of the sea" (33). The authors considered that seaside residents might be exposed to higher doses of radioactive material via inhalation of sea spray but considered this hypothesis implausible. They concluded that the high incidence of MM in Walney Island was due to chance.

Dioxin Levels. The Island of Walney borders the Irish Sea. PCB levels were reported for seals from the Liverpool Bay area of the Irish Sea (34). In three grey seals (*H. grypus*) examined in 1988, blubber values of PCBs ranged from 34 to 101 mg/kg wet weight total PCBs. The author concluded, "These values are considered to be high and approach those found in common seals in the polluted Dutch Wadden Sea" (34).

Comment. The case-control study described within this cluster is important because it represents an association between MM and proximity to bodies of water at the level of the individual. Because coastal dwellers are known to consume more fish than inland residents (35, 36), the association of MM with proximity to the sea may reflect increased fish consumption.

Baglan Bay, Wales. The sixth cluster of MM occurred in the vicinity of Baglan Bay, Wales. Concerns about clusters of cancer in the vicinity of the Baglan Bay petrochemical works led to an evaluation of cancer incidence and mortality in the 7.5-km area surrounding the plant. Although there was no excess of cancers overall, the investigators found a significant excess of MM (42 deaths observed; 28.3 expected), predominantly among women. The authors were unable to suggest a possible cause of this increased mortality.

Dioxin Levels. Baglan Bay, Wales is located near Baglan Bay and the Bristol Channel. Reports of dioxin levels in these bodies of water were not available. However, the petrochemical works in the vicinity would be expected to be a source of dioxins in the aquatic environment (37) (38).

T Town, Japan. The seventh MM cluster was reported by Kosaka *et al.* (39) in T Town, Japan. T Town is a small seaside community (population 9000) located at the mouth of a large river within the boundaries of Tokushima City. During the period 1978-1988, seven incident cases of MM (four males, three females) were observed in T Town for an annual age-adjusted incidence rate of 7.03 per 100,000 (8.31 in males and 4.46 in females), versus 1.20 in Tokushima City and 1.53 for Japan as a whole. None of the patients had a history of exposure to significant radiation, toxic chemicals, or chronic infection. Five of the seven patients had been fishermen since youth, and six had lived in a small area close to the fishing port near the river. The authors noted, "We were unable to find any etiologic factors in this group of fishermen, except for their abundant intake of sea food which could be polluted with some chemical agents." They observed, "all three communities which had myeloma clusters, namely Thief River Falls, Petersburg and T Town, are located close to large rivers," and suggested that "additional studies of myeloma clusters throughout the world

Table 1 Location of geographic clusters of multiple myeloma, adjacent bodies of water, and evidence of dioxin contamination

Location of cluster	Near body of water?	Body of water	Dioxin contamination
Thief River Falls, MN	Yes	Thief River; Red Lake River	ND ^a
Aberdeen, Scotland	Yes	Dee River; Don River; North Sea	++
Western Ireland	Yes	Atlantic Ocean	+
Petersburg, VA	Yes	James River; Appomattox River	++
South Cumbria, U.K.	Yes	Irish Sea	+
Baglan Bay, Wales	Yes	Baglan Bay; Bristol Channel	ND/+
T Town, Japan	Yes	Yoshino River; Osaka Bay	++
Okeechobee County, FL	Yes	Kissimmee River; Lake Okeechobee	++

^a ND, No data. Strength of evidence: ++, strong; +, moderate.

may provide further information on the etiology of this disease" (39).

Dioxin Levels. T Town, Japan is located near the Yoshino River and Osaka Bay. Measurements of dioxins in blue mussels (*Mytilus edulis*) demonstrate that a wide coastal area of Osaka Bay is polluted with dioxins. The average concentration of PCBs was 65 ppb (40). The main source of these dioxins is fly ash from municipal waste incinerators (41).

Studies of dietary dioxin intake of Japanese women from Osaka indicate that 176 of 177 of the daily diets analyzed were contaminated with PCBs. The daily intake of PCBs ranged from 0–334.0 µg/day and was highest among those who consumed fish (42). Thus, these data indicate that individuals who consume fish from Osaka Bay have high exposures to dioxins.

Okeechobee County, FL. The eighth MM cluster took place in Okeechobee County, Florida. During 1981–1993, 37 incident cases of MM were reported to the state cancer registry, for an annual age-adjusted incidence rate of 7.91 per 100,000, versus 3.46 for Florida. We confirmed both the diagnoses and the residential addresses for 30 of the cases. Twenty-eight of the cases were White. Fourteen cases were female. Using these verified cases only, the annual age-adjusted incidence rate for MM in Okeechobee County is 6.52 per 100,000, versus 3.44 for the rest of Florida (excluding Okeechobee County; $P < 0.001$). Examination of patients' medical records yielded no evidence of unusual prior radiation or history of cancer.

Examination of state agricultural reports reveals that Okeechobee County is remarkable in two respects. It is the largest source of dairy cattle in Florida, and it is the largest source of revenue from the sale of commercial fishing licenses (43). The latter reflects its proximity to Lake Okeechobee, the state's largest freshwater lake.

Dioxin Levels. Okeechobee, Florida is located in south/central Florida along the northern shore of Lake Okeechobee. Chlorinated hydrocarbon insecticides have been heavily applied in the agricultural economy of southern Florida. Surface runoff, including sediment and absorbed chlorinated hydrocarbons, is transported by a system of levees, canals, and water pumping stations from the Everglades into Lake Okeechobee. This has resulted in high dioxin levels in lake sediments (44). Maximum concentrations of dioxins in sediments of southern Florida were reported to be 6 µg/kg for dichlorodiphenyldichloroethane (DDD) and 9 µg/kg DDD (45).

In summary, we reviewed eight clusters of MM from diverse locations around the world (Table 1). All of the eight clusters were located proximate to a body of water. At least six of these bodies of water have been contaminated with dioxins. Data on dioxin contamination were not available for two sites. However, one of these sites (Baglan Bay) is proximate to an industrial activity known to be a source of dioxins.

For comparison, we evaluated proximity to water in 50 randomly selected "control" locations not associated with clusters of MM. Thirty-two of the 50 locations (64%) were associated with water. 18 (36%) were not. Thus, the probability that eight of eight sites would be associated with a body of water solely by chance is low ($P = 0.04$, Fisher's exact test).

The Dioxin Hypothesis

We suggest that a plausible explanation for the association of MM with proximity to bodies of water is the following:

- (a) Dioxin contamination of water results in the accumulation of dioxins in fish and seafood;
- (b) High consumers of fish and seafood have elevated body levels of dioxins; and
- (c) Humans with high exposures to dioxins are at increased risk for MM.

The evidence for (a) has already been addressed (12–14). The evidence for (b) and (c) is summarized below.

(b) High Consumers of Fish and Seafood Have Elevated Body Levels of Dioxins

Data from several populations indicate that the consumption of dioxin-contaminated fish is associated with elevated levels of dioxins in blood. For example, serum PCB levels in Japanese men increased almost 2-fold (e.g., from 2.5 to 4.0 ppb) several hours after consuming fish containing 181 µg of PCBs (46). Additionally, mean serum PCB and DDT levels were significantly higher in consumers of Great Lakes sports fish than in controls: 19.0 versus 6.8 ppb for PCB; 15.6 versus 6.8 ppb DDT; 112 fish-eaters versus 95 controls; Ref. 47). Similar findings have been observed among fish-eaters in Sweden (48). Even greater differences in serum dioxin levels between fish-eaters and non fish-eaters were reported among the Inuit. Dewailly et al. (49) found that the total dioxin toxic equivalents among 10 fishermen with high consumption of fish from the contaminated St. Lawrence River were 900 ng/kg compared to 36 ng/kg for controls.

Svensson et al. (50) measured reported fish consumption and exposure to persistent organochlorine compounds in two cohorts of Swedish fishermen. The fishermen as a group ate almost twice as much fish as non-fishermen referents from the general Swedish population. Fishermen from the eastcoast (Baltic Sea), which is heavily polluted with dioxins, ate more fatty fish (salmon and herring) than fishermen from the relatively unpolluted westcoast. Eastcoast fishermen had 2–6 times higher total dioxin toxic equivalents of PCDD/PCDF and PCBs in their plasma than both westcoast fishermen and non-fishermen referents from the east and westcoasts. Thus, blood levels of dioxins in fishermen were proportional to the estimated consumption of dioxin-contaminated fish.

(c) Human Increase

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(c) Humans with High Exposures to Dioxins Are at Increased Risk for MM

The dioxin hypothesis predicts that individuals with high consumption of dioxin-contaminated fish should be at increased risk for MM. We are not aware of any epidemiological studies that have evaluated the risk of MM with respect to this factor in individuals. However, epidemiological data exist for two groups that have high exposures to dioxin-contaminated fish: Alaskan Natives and Swedish fishermen.

Alaskan Natives. Because of their diet high in fish and sea mammals (11), Alaskan Natives comprise a natural experiment of the dioxin hypothesis. The Alaskan Native population includes Inuits (Eskimos), Indians, and Aleuts. The majority of dietary information on Alaskan Natives concerns the Inuit, although the diets of Indians and Aleuts are similar with respect to the high consumption of fish and marine mammals (52).

The Inuit diet is known to have high levels of organochlorine contaminants, and these contaminants are present in high concentrations in blood and other tissues (53). Cancer incidence among Alaskan Natives was studied by Alberts and Lanier (54). Compared to U.S. Whites, incidence rates were low for lymphoma and leukemia but not for MM. These authors noted, "Whereas the rate for all Alaskan Native males combined was similar to U.S. and European rates, the rates for Indian males from the southeastern Alaska tribes appear to be even higher than the high incidence reported for black Americans" (54). High rates for MM were not found among women. It is intriguing in this regard that dietary studies have shown that the average Inuit woman's diet contains less than one-third of the organochlorine contaminants present in the diets of males (55). Additionally, women may significantly lower their body burden of organochlorine compounds via breastfeeding (56). Thus, these data suggest that high dietary intake of dioxins may be associated with an increased risk of MM, at least among Alaskan Indian males.

Swedish Fishermen. Svensson *et al.* (57) and Hagmar *et al.* (58) compared cancer incidence and mortality between east-coast (*i.e.*, dioxin exposed) and westcoast cohorts of Swedish fishermen and the general Swedish population. Compared with the regional population and the westcoast fishermen, the east-coast fishermen showed "suggestive increases of myelomas (Standardized Incidence Ratio, 2.08; 95% CI, 0.76–4.53)." Moreover, mortality from MM was significantly increased among the eastcoast fishermen as compared with the westcoast fishermen (Incidence Rate Ratio, 3.2; 95% CI, 1.2–8.7) and with that of the general population (Standardized Mortality Ratio, 3.1; 95% CI, 1.2–6.4). The authors offered no explanation for this finding but noted a similar increased risk for MM among Swedish farmers (59). A subsequent population-based study in Sweden found that exposure to two pesticides, phenoxyacetic acid and DDT, was a significant risk factor for MM (60). Thus, these data support the hypothesis that exposure to dioxins increases the risk of MM (61).

Seveso, Italy. The dioxin hypothesis predicts that individuals exposed to high levels of dioxins through other forms of environmental pollution also would have an increased risk of MM. Numerous epidemiological studies have focused on persons with potential exposure to dioxins through manufacturing, during wartime, or following industrial accidents. However, many of these studies are subject to potentially severe misclassification bias caused by the use of indirect historical measurements of exposure (62–64). Follow-up on the population living near Seveso, Italy is relevant in this regard. In 1976, an accidental

explosion in a chemical plant exposed the local population to the highest documented human exposure to TCDD.

The incidence of cancer in Seveso was evaluated by Bertazzi *et al.* (65) for the decade following the accident. Among males, the authors found a significantly increased risk for lymphoreticulosarcoma, a form of NHL (ICD 9 Code 200; RR, 5.7; 95% CI, 1.7–19), and an elevated risk for MM (RR, 3.2; CI, 0.8–13.3, based on two cases). Women showed an increased risk for cancers of the hematopoietic system and a significantly increased risk for MM (RR, 5.3; CI, 1.2–22.6, based on two cases). Recently, a large occupational cohort study in Germany among male workers known to be exposed to TCDD also found a significantly increased risk of MM (SMR, 543; CI, 111–1587, based on three deaths; Ref. 66). Thus, these data provide additional support for the dioxin hypothesis.

Biological Plausibility

The evidence summarized above demonstrates that occupational and environmental exposures to dioxins are associated with an increased risk of MM. We now address the question, "Are dioxins biologically plausible myelomagens?"

Dioxins have been associated with NHL (67–69). Because NHL and MM are both neoplasms of B cells, these malignancies may have risk factors in common. Moreover, extensive laboratory evidence indicates that dioxins are immunotoxic and that B cells are especially sensitive to their effects (70–72). This evidence includes the following. Exposure of murine B cells to TCDD causes an increase in the activation of resting B cells and an increase in the secretion of IgM in the absence of antigen (73). In addition, TCDD inhibits the differentiation of murine B cells into antibody secreting cells *in vitro* (74) and *in vivo* (75). Similar findings have been observed in human B lymphocytes (76). Furthermore, TCDD exposure in adult mice causes a depression in B cell-mediated immunity that results in decreased host resistance to the non-lethal parasite, *Plasmodium yoelli* (77). This observation resembles the increased risk of infection seen in patients with MM caused by decreased levels of normal immunoglobulins (78).

In summary, dioxins can cause many of the B-cell abnormalities that are characteristic of MM. These abnormalities often have been interpreted as evidence of "chronic antigenic stimulation." In contrast, dioxins can produce the apparent effects of "chronic antigenic stimulation" and can do so without antigens.

Discussion

The goals of this paper are to: (a) draw attention to an association between clusters of MM and bodies of water; and (b) construct an etiological hypothesis for MM that could explain this association. We hypothesize that these clusters reflect exposure to dioxins, especially via the consumption of dioxin-contaminated fish and seafood. Other possible explanations for this association include chance and confounding.

Because bodies of water are common, the association of MM with bodies of water may be coincidental. However, our estimate of the prevalence of proximity to bodies of water in "control" locations (32 of 50) suggests that the observed prevalence in the MM clusters (8 of 8) is unlikely to have occurred solely by chance. Moreover, in addition to the association between MM and proximity to bodies of water at the level of the cluster, the case-control study in South Cumbria found a significant association at the level of the individual (33). Although this association also may be due to chance, a hypothesis

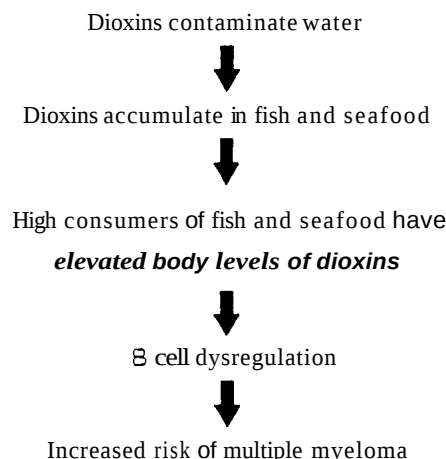


Fig. 1. Summary of the dioxin hypothesis for the etiology of MM

linking risk of MM to proximity to bodies of water offers a more consistent explanation of these findings.

Two clusters were located in proximity to nuclear establishments. Because ionizing radiation is a risk factor for MM, it is possible that these clusters are a direct consequence of increased radiation near these installations. This hypothesis is plausible but was not supported by estimates of radiation made during these investigations. Moreover, to our knowledge, the other six sites are not located in the vicinity of similar installations. Thus, a hypothesis involving some exposure to water provides a more coherent explanation for the similarities among the clusters.

There are many pollutants in water other than dioxins that could be potential myelomagens. For example, mercury is a common aquatic pollutant and is known to have immunosuppressive effects in animals (79). However, mercury contamination was not a feature shared by the MM clusters we reviewed. Moreover, unlike blood levels of dioxins, measurements of blood mercury levels did not differ between the cohorts of Swedish fishermen with significantly different risks for MM (50). Thus, although there may be other possible causes of MM that are associated with water, dioxins appear to provide the conceptual "best fit" to these observations. The dioxin hypothesis is summarized in Fig. 1.

The dioxin hypothesis is consistent with many other observations concerning MM. For example, Friedman and Hemnton (80) reported an unanticipated association between obesity and the development of MM. This finding, they noted, could result from "the increased storage and subsequent mobilization of fat-soluble pesticides, pesticide metabolites, or other potential carcinogens in the adipose tissue of obese persons" (80).

The dioxin hypothesis also makes predictions about place and time. Thus, dioxin levels are known to be elevated in fish and shellfish collected at sites near discharges from pulp/paper manufacturing (37). It is intriguing in this regard that ecological studies have shown elevated mortality rates from MM in these areas (81). In addition, the rapid increase in MM incidence and mortality in industrial societies since 1950, especially in Japan (82), is consistent with temporal trends in the manufacture of chlorinated organic chemicals.

Finally, the dioxin hypothesis suggests new opportunities for analytic studies of the monoclonal gammopathies. For ex-

ample, cases with MM should report greater consumption of fish from contaminated waters than non-MM controls. Similarly, the incidence of MM should be higher in individuals with high consumption of dioxin-contaminated fish. Because dioxins have been shown to inhibit the differentiation of immunoglobulin-producing cells (73), other monoclonal gammopathies also may be more common among dioxin-exposed individuals. For example, MGUS denotes the presence of increased levels of immunoglobulins in asymptomatic persons and is the most common monoclonal gammopathy (83). Because the incidence of MGUS is greater than the incidence of MM, the dioxin hypothesis may be more easily tested among persons with MGUS.

Because dioxins are stable and have long half-lives, the dioxin hypothesis is amenable to molecular epidemiological study. For example, Hardell and colleagues compared PCDD and PCDF concentrations in adipose tissue from 7 patients with "malignant lymphoproliferative diseases" (6 NHL and 1 plasmacytoma) to 12 surgical patients without malignancy (84). The concentrations of dioxins in the patients with lymphoproliferative malignancy were significantly higher. Because patients with lymphoproliferative disease were selected to participate because of their greater dioxin exposure, this was not a case-control study. However, this study illustrates that molecular epidemiological studies of MM are feasible and suggests that the observed differences may be etiologically important.

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Abstract

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