Letters to the Editor

Correspondence re: G. G. Schwartz, Multiple Myeloma: Clusters, Clues, and Dioxins. Cancer Epidemiol. Biomark. Prev., *6:* 49–56, 1997.

Letter

Steven R. Alberts and Anne P. Lanier

Department of Oncology, Mayo Clinic, Rochester, Minnesota 55905 [S. R. A.], and Alaska Native Health Board, Anchorage, Alaska 99508 [A. P. L.]

We read with interest the paper entitled "Multiple Myeloma: Clusters, Clues, and Dioxins" by Dr. Gary G. Schwartz (1). Dr. Schwartz has constructed an interesting hypothesis in regard to a possible association between dioxin exposure and the subsequent risk of developing multiple myeloma. Dr. Schwartz has gathered a number of apparent clusters of multiple myeloma from the literature, together with studies assessing dioxin levels in various parts of the world, to suggest such an association. However, we are concerned about the manner in which this information has been presented to support his hypothesis, particularly as it pertains to multiple myeloma in southeast Alaska Indians and the consumption of food items contaminated with dioxins. We would like to take this opportunity to respond to the proposed hypothesis with regard to multiple myeloma in Alaska Natives.

Alaska Natives include Eskimos, Aleuts, and Indians. There are four Eskimo linguistic groups and at least four groups of Indians (Athabascans of central Alaska and Tlingit, Haida, and Tsimpsian of southeast Alaska). As we previously reported, multiple myeloma appears to occur at a high rate in southeast Alaska Indian males (2). This increased incidence has been reconfirmed in subsequent reviews of cancer incidence in Alaska Natives covering the period 1969–1993 (3, 4). However, multiple myeloma in the remainder of the Alaska Native community occurs at a low rate compared to the incidence of multiple myeloma for the general United States population (2–4). In particular, multiple myeloma rates are low for the Eskimos (Inupiat and Yupik) of Alaska. Yet, Eskimos have traditionally consumed marine biota as a major part of their diet, including marine mammals (5, 6). The incidence of multiple myeloma is also low in the circumpolar Inuit (7). It is particularly important to note that no cases of multiple myeloma have ever been reported in the Inuit of Canada.

Dr. Schwartz has correctly cited the study by Dewailly *et al.* (8) showing increased concentrations of organochlorines among the Inuit of the eastern Arctic in Canada. Increased levels of dioxins in fish, marine mammals, and polar bears, as well as in the Inuit, have been well documented (8, 9). However, it is difficult to understand how Dr. Schwartz can make an association between data collected on the levels of organochlorines from the eastern Arctic of Canada and multiple myeloma in the Indians of southeast Alaska. We are aware of no studies that have assessed the levels of organochlorines in Alaska Natives residing in southeast Alaska or in foods uniquely used by that population. Thus, we do not feel that the epidemiology of multiple myeloma in Alaska Natives or in the Inuit across the Arctic support Dr. Schwartz's hypothesis.

The apparent high incidence of multiple myeloma in southeast Alaska Indian males is of concern. However, it must be noted that this incidence is based on nine cases of multiple myeloma over a 25-year period (4). As we previously stated in our paper (2), incidence rates derived from such small numbers must be interpreted with caution. It is important that the incidence of multiple myeloma among Alaska Natives continues to be monitored and that possible etiologies of this disease are investigated.

References

1. Schwartz, G. G. Multiple myeloma: clusters, clues, and dioxins. Cancer Epidemiol. Biomark. Prev., *6:* 49–56, 1997.

2. Alberts, S. R., and Lanier A. P. Leukemia, lymphoma, and multiple myeloma in Alaskan Natives. J. Natl. Cancer Inst. (Bethesda), *78:* 831–837, 1987.

3. Lanier, A. P., Bulkow, L. R., and Ireland, B. Cancer in Alaskan Indians, Eskimos, and Aleuts, 1969–83: implications for etiology and control. Public Health Rep., *104:* 658–664, 1989.

4. Lanier, A. P., Kelly, J., Smith, B., Amadon, C., Harpster, A., Peters, H., Tanttila, H., Key, C., and Davidson, A. M. Cancer in Alaska Natives 1969–1993. 25 Year Report. Alaska Area Native Health Service, Indian Health Service, 1996.

5. Nobmann, E. D., Byers, T., Lanier, A. P., Hankins, J. H., and Jackson, M. Y. The diet of Alaska Native adults: 1987–1988. Am. J. Clin. Nutr., *55:* 1024–1032, 1992.

6. Heller, C. A., and Scott, E. M. The Alaska dietary survey, 1956–1961, Public Health Service publ. No. 999-AH-2. Anchorage, AK: Arctic Health Research Center, Nutrition and Metabolic Disease Section, Public Health Service, DHEW, 1967.

7. Lanier, A. P., and Alberts, S. R. Malignant neoplasms of the lymphatic and haematopoietic system in Circumpolar Inuit. Acta Oncol., *35:* 601–606, 1996.

8. Dewailly, E., Ayotte, P., Brunneau, S., Laliberte, C., Muir, D. C. G., and Norstrom, R. J. Inuit exposure to organochlorines through the aquatic food chain in Arctic Quebec. Environ. Health Perspect., *101:* 618–620, 1993.

9. Kuhnlein, H. V., Receveur, O., Muir, D. C. G., Chan, H. M., and Soueida, R. Arctic indigenous women consume greater than acceptable levels of organochlorines. J. Nutr., *125:* 2501–2510, 1995.

Received 5/19/97; accepted 6/10/97.

Reply

Gary G. Schwartz

Sylvester Comprehensive Cancer Center and Department of Epidemiology and Public Health, University of Miami School of Medicine, Miami, Florida 33101

We thank Dr. Alberts for his interest in our hypothesis. Dr. Alberts points out that multiple myeloma appears to occur at a high rate in southeast Alaska Indian males and not, apparently, in other presumably dioxin-exposed Alaska Native populations, a point acknowledged in our paper (1). We would like to respond to his conclusion that "the epidemiology of multiple myeloma in Alaska Native populations or in the Inuit across the Arctic" does not support the dioxin hypothesis.

Received 6/10/97; accepted 6/10/97.

As Dr. Alberts notes, we developed the dioxin hypothesis on the basis of our evaluation of dioxin levels in defined geographic clusters of multiple myeloma. Those data, we believe, clearly demonstrate the existence of an association between clusters of multiple myeloma and environmental dioxins. Given that association, the hypothesis compelled us to examine whether other populations known (or strongly suspected) to have high exposures to dioxins also had increased risks for multiple myeloma. It is in this context, one of prediction or hypothesis testing, that the significantly elevated risks of multiple myeloma among southeast Alaska Indian males (2), among persons in occupations with potential exposure to dioxins (3), among cohorts of dioxin-exposed *versus* dioxin-unexposed fishermen (4), and among populations exposed to dioxins in industrial accidents in Sveso, Italy (5) and in Germany (6) are informative and seem decidedly confirmatory. That is, the dioxin hypothesis predicts that, in general, populations with elevated exposures to dioxins should have elevated rates of multiple myeloma. It does not require that every population of dioxin-exposed Alaska Natives or Inuits have elevated rates.

There are several reasons why some dioxin-exposed populations may have incidence rates for multiple myeloma that are lower than expected. The most obvious of these is the potential for underdiagnosis of a rare disease in remote and medically underserved populations, such as many Alaska Native communities. In addition, the median age at diagnosis for multiple myeloma in many hospital series is 69 (7). According to the 1980 census, only 6% of the Alaska Native population of 64,000 was over the age of 60 (8). Thus, the power to detect an increased risk of multiple myeloma in this population may be small. Lastly, we note that the toxic effects of dioxins are mediated via a specific intracellular protein, the aryl hydrocarbon receptor (AhR; Ref. 9). Genetic strains of mice with high-affinity AhRs are more sensitive to the immunotoxic effects of dioxins than are strains with lower-affinity AhRs (10), and mice lacking the AhR are entirely resistant (11). Genetic factors that mediate sensitivity to dioxins in humans may be relevant to the risk of multiple myeloma in dioxin-exposed populations (12).

References

1. Schwartz, G. G. Multiple myeloma: Clusters, clues, and dioxins. Cancer Epidemiol. Biomark. Prev., *6:* 49–56, 1997.

2. Alberts, S. R., and Lanier, A. P. Leukemia, lymphoma, and multiple myeloma in Alaskan natives. J. Natl. Cancer Inst. (Bethesda), *78:* 831–837, 1987.

3. Eriksson, M., Hardell, L., Malker, H., and Weiner, J. Malignant lymphoproliferative diseases in occupations with potential exposure to phenoxyacetic acids or dioxins: a registry-based study. Am. J. Ind. Med., *22:* 305–312, 1992.

4. Svensson, B-G., Miloczy, Z., Strömberg, U., and Hagmar, L. Mortality and cancer incidence among Swedish fishermen with a high dietary intake of persistent organochlorine compounds. Scand. J. Work Environ. Health, *21:* 106–115, 1995.

5. Bertazzi, A., Pesatori, A. C., Consonni, D., Tironi, A., Landi, M. T., and Zochetti, C. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. Epidemiology, *4:* 398–406, 1993.

6. Becher, H., Flesch-Janys, D., Kauppinen, T., Kogevinas, M., Steindorf, K., Manz, A., and Wahrendorf, J. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Cancer Causes Control, *7:* 312–321, 1996.

7. Gautier, M., and Cohen, H. J. Multiple myeloma in the elderly. J. Am. Geriatr. Soc., *42:* 653–664.

8. Lanier, A. P. Cancer in circumpolar Inuit: background information for Alaska. Acta Oncol., *35:* 523–525, 1996.

9. Poland, A., and Knutson, J. C. 2,3,7,8-Tetrachlorodibezo-*p*-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity. Annu. Rev. Pharmacol. Toxicol., *22:* 517–554, 1982.

10. Kerkvliet, N. I. Immunological effects of chlorinated dibenzo-*p*-dioxins. Environ. Health Perspect., *103* (Suppl. 9): 47–53, 1995.

11. Fernandez-Salguero, P. M., Hilbert, D. M., Rudikoff, S., Ward, J. M., and Gonzalez, F. J. Aryl-hydrocarbon receptor-deficient mice are resistant to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced toxicity. Toxicol. Appl. Pharmacol., *140:* 173–179.

12. Geyer, H. J., Schramm, K. W., Scheunert, I., Schugart, K., Buter, J., Wurst, W., Greim, H., Kluge, R., Steinberg, C. E. W., Kettrup, A., Madhukar, B., Olson, J. R., and Ballo, M. A. Considerations on genetic and environmental factors that contribute to resistance or sensitivity of mammals including humans to toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds. 1. Genetic factors affecting the toxicity of TCDD. Ecotox. Environ. Safety, *36:* 213–230, 1997.