ranging from about 1% per year to 4% per year depending on age. If these increases are real they are of some concern.

Support for the hypothesis that these increases are not just better reporting is provided by the cohort plot shown elsewhere in this volume.[2] The increase in multiple myeloma death rate from older to younger cohorts in the United States appears as an upward shift in the cohort curve, which remains linear and consistent with a multiple hit model for all cohorts. This may not be the case in other countries, where the reported rates of increase are much higher.[5] The accuracy of ascertainment for multiple myeloma is also quite high, exceeding 97% in the SEER program in 1985 and 1986.[6]

In sum, the available evidence strongly suggests that the observed increases in multiple myeloma death rates are real. The parallel increases in both sexes argues against an occupational cause. While the regressions show larger rates of increases in the elderly, the cohort plot indicates a parallel leftward shift to higher death rates at all ages. The rate of increase is slowing in younger ages because the cohort of maximum risk has already attained those ages. This suggests a general environmental exposure, common to all industrial countries and which increased during the latter quarter of the 19th century and first quarter of this century. This was a period characterized by the rapid increase in uncontrolled coal combustion and other industrial activity. These factors need further examination to clarify their potential role.

SUMMARY

Reported mortality rates from multiple myeloma have been increasing in all industrialized countries in the last 20 years. The rate of increase shows a strong interaction with age: it is slow in persons aged 55 to 59, and increases steadily with increasing age to reach rates of increase in excess of 4% per year in persons 85 years and older. The rate of increase is moderately consistent across sexes and countries. Multiple myeloma is one of the best ascertained cancers, which argues against better ascertainment as the sole cause of the increasing trend. Cohort plots in the United States suggest a parallel shift upward in risk between the birth cohorts of 1870 and 1910, with no evidence of differential effects in the elderly. This suggests a real increase is occurring as a result of some general environmental factors.

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Is Exposure to Benzene a Cause of Human Multiple Myeloma?[a]

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INTRODUCTION

In this article I argue that it is reasonable, although not scientifically proven, to causally relate benzene exposure to multiple myeloma. The evidence remains less than definitive in that the level of proof of such a relationship does not meet that required for a statement of scientific certainty, although it is rapidly approaching this point.

DESCRIPTION OF MULTIPLE MYELOMA

Multiple myeloma is a tumor of plasma cells.[1,2] These are antibody-producing cells derived from B lymphocytes, which are located primarily in the bone marrow. For the most part, the tumors are diffusely present within bone marrow, although occasionally individual tumors are found in extramedullary sites. Despite this diffuse presence within marrow-containing bone, in almost all cases myeloma begins with a somatic mutation in a single cell. This is evident from a major diagnostic test for this disease, the presence of a monoclonal antibody demonstrable on a serum protein electrophoresis. Analysis of this protein reveals that it is uniform in its chemical composition, an elegant example of the origin of cancer in a single aberrant proliferative cell. Definitive diagnosis of multiple myeloma depends on the presence of an increased number of plasma cells, sometimes with abnormal morphology, in the bone marrow. Occasionally, an individual with an abnormal serum protein electrophoresis is observed who does not have bone marrow or other clinical findings consistent with multiple myeloma. These individuals with "benign monoclonal gammopathy" will occasionally progress to classic multiple myeloma.

IS MULTIPLE MYELOMA INCREASING IN INCIDENCE?

Under discussion in this volume is an apparent increase in the incidence of multiple myeloma, particularly among older age groups. The serum protein electrophoresis test for multiple myeloma has been available for approximately three decades. It is

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a relatively routinely used laboratory procedure as it provides information about a variety of serum proteins and is pertinent to diseases other than multiple myeloma. There is little reason to expect that diagnostic ability has improved during this period, although one could argue that a young individual with bone pain, unusual fracture, or anemia might be more likely to have a serum protein electrophoresis ordered by a physician than would an elderly individual. However, this can not be a substantial factor inasmuch as there has been relatively little change in the life-span of individuals diagnosed with multiple myeloma, despite the development of very valuable chemotherapeutic approaches that have had a major impact on decreasing the morbidity associated with this disease.[2] Earlier diagnosis, even with no improvement in chemotherapy, should show up as a prolongation of survival. Accordingly, in my judgment, it is doubtful but not inconceivable that a significant increase in diagnostic ability for multiple myeloma has occurred.

Velez *et al.* have reviewed trends in multiple myeloma incidence.[3] They concluded that technical improvements in diagnosis and increased access to medical care have contributed to an increased incidence of myeloma but that the observed increase may be partly real. Of interest is that Percy *et al.* have recently reported that of all cancers, multiple myeloma is most accurately listed on death certificates.[4]

BENZENE HEMATOTOXICITY

Benzene is a bone marrow toxin, producing destruction of the bone marrow, known as aplastic anemia, in a dose-responsive fashion.[5,6] Benzene is also a known human leukemogen, causing acute myelogenous leukemia (AML) and its variants, such as acute myelomonocytic leukemia, acute promyelocytic leukemia, and erythroleukemia.[6,7] Based primarily on case reports, benzene has also been causally related to a variety of other hematological neoplasms, including chronic myelogenous leukemia and non-Hodgkin's lymphoma, as well as multiple myeloma.[6-9]

The evidence relating benzene to AML originally was based on the multiplicity of cases in which patients with benzene-induced aplastic anemia were followed through a preleukemic phase until the eventual development of AML (a process that now goes under the term myelodysplastic syndrome). In addition, hematologists accepted benzene as being causally related to AML because of a variety of pieces of evidence that fit under the heading of biomedical plausibility. These include the observation that transformation of aplastic anemia into AML was not uncommon with any agent that caused aplastic anemia, and that benzene readily produced chromosomal abnormalities following human exposure.[10] More recently, classic epidemiological studies have confirmed the causal relation between benzene and AML.[11,12]

BENZENE TOXICOLOGY

Benzene itself is not a direct bone marrow toxin but must be metabolized to produce its effects.[5,6] There is some evidence to suggest that a toxic intermediate is formed in the liver and travels to the bone marrow.[13] Although there has been much research on the subject, the specific biological reactive intermediate(s) responsible for bone marrow toxicity, or for leukemia, is unknown. Recent animal studies have

demonstrated that benzene is a carcinogen, producing a variety of solid tumors and lymphatic tumors.[14,15] A satisfactory animal model of benzene-induced acute myelogenous leukemia is still lacking. Among the earliest effects of benzene in laboratory animals and in occupationally exposed groups is a decrease in lymphocyte amount.[16,17] In laboratory animals, this appears to affect both B and T lymphocytes and to lead at higher doses to a melting away of lymphoid tissues.[16,17]

RELATION OF BENZENE TO MULTIPLE MYELOMA

The question of the causal relationship between benzene and multiple myeloma can be considered under two headings, the biomedical background underlying the plausibility of the association and the human data reporting multiple myeloma in benzene-exposed populations.

Biomedical Plausibility

There is a high level of biomedical plausibility supporting a causal relationship between benzene exposure and multiple myeloma. Biolcgical reactive intermediates of benzene are carcinogenic within the bone marrow, and plasma cells are located within the bone marrow. The basic cell type of plasma cells, the B lymphocyte, is affected by benzene and is probably the circulating lymphocytic cell found to have benzene-induced cytogenetic abnormalities. Thus, we have a carcinogen that is specific to the organ at risk and affects the basic cell type, including producing cytogenetic abnormalities.

Human Findings

It is more difficult to establish a causal relationship of benzene with human multiple myeloma than it is with AML for two major reasons: the background incidence of multiple myeloma is only one-third to one-half that of AML, and, as usually a slower growing tumor, the lag period between exposure and the development of clinically overt multiple myeloma is presumably longer than it is for AML.

Case reports of multiple myeloma in benzene-exposed individuals include two reported by Torres *et al.* and four cases by Aksoy.[20,21] Among the latter is one case from a cohort that was noted to have an increased incidence of aplastic anemia after introduction in the 1960s of a benzene-containing glue in the Turkish leather industry.[3] This was followed by a wave of acute myelogenous leukemia and Professor Aksoy and his colleagues are now observing cases of multiple myeloma in this group and among other workers chronically exposed to benzene. These four cases were exposed to benzene for 7 to 35 years (mean 18 years), a much longer period of exposure than that observed for the shoemakers with acute myelogenous leukemia. Yin, in China, has also noted cases of multiple myeloma in his large cohort of benzene-exposed workers that are now undergoing more thorough epidemiolog calanalysis.[22]

There are a number of epidemiological studies that have some suggestion of an increased risk of multiple myeloma among benzene-exposed workers. Cohort studies include that of Decouflé *et al.* of 259 male employees of a chemical plant.[23] Of 58 deaths, four were due to lymphoreticular tumors with 1.1 expected (95% confidence limits 1.09–10.24). Of these, one death was due to multiple myeloma and a second, recorded as acute myelomonocytic leukemia, was an individual with multiple myeloma who developed leukemia two years following the institution of therapy for myeloma with alkylating agents, a recognized complication of myeloma treatment.

The most thoroughly studied cohort of benzene-exposed individuals is that of pliofilm workers in Akron, Ohio who have been extensively evaluated by National Institute of Occupational Safety and Health scientists.[11,24] Their initial report in 1976 noted seven cases of myelogenous leukemia in a cohort of 748 workers in which only 1.38 was expected. In their most recent follow-up in 1987, there are now nine cases of myelogenous leukemia with 2.7 expected. In addition, four cases of multiple myeloma have been noted with 1.0 expected (SMR 409; 95% confidence interval 110–1,047). The four cases were not from the most heavily exposed group, leading to speculation that relatively low cumulative exposures may produce a relatively well-differentiated tumor such as multiple myeloma. However, as somewhere between one to three of these cases presumably would have occurred by chance, it is difficult to draw any conclusions from dose considerations.

There are hints of higher than expected multiple myeloma incidence in other cohorts of benzene-exposed workers. While there are relatively many large cohorts of potentially benzene-exposed workers in the literature, attempting a "meta analysis" is difficult, particularly as there is a relatively low background incidence of multiple myeloma, and in published studies it is frequently lumped together with a group of other, even rarer, hematological tumors. Further, the extent of benzene exposure in larger cohorts is difficult to determine. Thus, Rushton and Alderson, in one of the largest studies of its kind, found a standardized mortality ratio (SMR) of 0.94 for all leukemia (30 observed, 32 expected) in evaluating 7,147 deaths among oil refinery workers in Britain in which the usual "healthy worker effect" was observed (SMR 0.89 for all cancers).[25] However, a follow-up case control study of these leukemia deaths observed a statistically significant association with benzene exposure.[26] Of potential interest is that the SMR for multiple myeloma in this same cohort was 1.07 (11 observed, 10.25 expected). It is open to question whether this smaller number would permit a nested case control study evaluating benzene exposure.

If one uses a SMR > 1.0 for leukemia as a possible marker of benzene exposure in a cohort, there are a number of other relatively large work groups in which the SMR for multiple myeloma is also above 1.0. For example, Delzell and Monson in a study of 6,533 men employed in the industrial products division of a rubber company found a statistically significant increase in multiple myeloma (10 observed, 4.4 expected) as well as lymphoma (10 observed, 4.3 expected).[27] For leukemia, 22 cases were observed while 21 were expected. Of note is that myeloma incidence was particularly elevated in workers who began work between 1935 and 1944. As Delzell and Monson did not evaluate deaths occurring before 1940, it is conceivable that a high level of benzene exposure in the 1930s led to undiscovered cases of benzene-induced leukemia before 1940, while the longer latency period led to myeloma not being observed until during the window of this study. Obviously, other explanations, including a lack of relation to benzene exposure, are possible.

A variety of case control studies have attempted to find clues for the etiology of

multiple myeloma. Morris *et al.* have reported an increased relative risk of multiple myeloma among individuals exposed to a variety of chemicals, including solvents.[28] Painters and carpenters also seemed to have a relatively high risk in a study by Friedman that also tended to confirm the previously reported causal role of radiation in myeloma.[29]

Overall, these findings are not sufficient to make an unequivocal statement that benzene is a cause of multiple myeloma. However, they raise the strong presumption of such a causal link and, in my judgment, it is now more likely than not that benzene exposure is an etiological factor in multiple myeloma. This does not necessarily mean that any increase in the incidence of multiple myeloma in recent years can necessarily be ascribed to benzene use, but it does raise an issue that needs to be considered.

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DISCUSSION

BERNARD D. GOLDSTEIN (*Robert Wood Johnson Medical School, Piscataway, NJ*): We started out discussing tumors with known etiology. There was a level of comfort in that discussion that simply wasn't present in our most recent discussion because we really don't quite know the etiology.

Multiple myeloma is one of these diseases where we also do not know the etiology despite a readily identifiable tumor. I'm going to present some arguments that benzene could be a contributing cause of multiple myeloma. If I were asked from the point of view of a reasonable medical probability rather than a scientific acceptance, I would say that it is reasonably, medically probable that benzene can cause multiple myeloma.

PHILIP LANDRIGAN (*Mount Sinai Medical Center, New York, NY*): I would like to pursue the issue of benzene exposure and myeloma and speculate on how exposure to benzene may account for these increasing trends. One of the interesting observations that came out of the Rinsky cohort of persons exposed to benzene that I worked on was that the four cases of myeloma in that cohort not only represented what was a fourfold excess over the expectation of approximately one case, but they tended to occur in people who had relatively less exposure than the people who developed leukemia within the same cohort. As we reported in the *New England Journal of Medicine*, multiple myeloma, the cause of death in four members of this cohort, has been observed previously in persons exposed to benzene, although also in small numbers (Decouflé *et al.* 1983. *Environ. Res.* 30: 16–25). In addition, several recent toxicologic studies have demonstrated lymphoid cancers in both rats and mice exposed to benzene (Snyder *et al.* 1980. *Toxicol. Appl. Pharmacol.* 54: 323–331; Maltoni *et al.* 1983. *Am. J. Ind. Med.* 4: 589–630; National Toxicology Program. 1986. NIH Publ. No. 86-2545). It is of interest that three of the four deaths from multiple myeloma that were observed in this cohort occurred in the group with the lowest cumulative exposure to benzene (<40 ppm-yr), and that all four persons who died had exceptionally long latency periods for hematologic cancer (>20 yr). These two observations raise the possibility that relatively low cumulative exposures to benzene may produce a relatively well-differentiated cancer, such as multiple myeloma, whereas higher exposures may lead to leukemia.

Thus, we speculated in the *NEJM* article, that low-dose chronic benzene exposure may produce myeloma, whereas high-dose exposure causes leukemia. This is a possibility that needs experimental verification. If true, it would offer an explanation for the observation that Olav Axelson mentioned. As I understand from his data, there was no increase in leukemia in people who were exposed to automobile exhaust, but there was an increase in multiple myeloma. This finding could account for the rising increase in the incidence of myeloma in the population at large.

A great deal of benzene exposure occurs at large in the population. Unleaded gasoline now contains as much as 4 or 5% benzene, at least in the U.S. Not all of it is combusted to carbon dioxide and water. Some of it vaporizes. People are exposed when they pump gas and are also exposed to emissions from incomplete combustion in car engines. It may be time to begin to do some first-stage hypothesis-generating ecologic studies in which atmospheric concentrations of benzenes in different cities, gasoline consumption, and the proportion of benzene in gasoline in different countries are compared with myeloma rates.

JOEL SCHWARTZ (*Environmental Protection Agency, Washington, D.C.*): Connie Percy asks what I mean by this change in ICD code. I mean that between the eighth revision and the ninth revision there is sometimes a change in the way people classify things; as a result of that, as we saw in Germany and we also see in Italy, there is a sudden discontinuous change in the reported rates of death in 203.

DEVRA DAVIS (*National Research Council, Washington, D.C.*): Solitary plasmacytoma in Italy and Germany turned out to be nearly half of the myelomas in the eighth ICD when these were removed from 203 in the ninth. This introduced the artifact of that downward curve you see with Italy, West Germany, and Sweden.

In fact, the tenth ICD revision conference places solitary plasmacytoma back into the code 203 for myeloma so this wrinkle will be smoothed out.

On the age issue, Dr. Cuzick did not use anyone over 75. Can you tell us about the quality of data in England for people 75 to 84 years of age particularly with respect to