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EL PASO MULTIPLE SCLEROSIS CLUSTER INVESTIGATION
EL PASO, EL PASO COUNTY, TEXAS

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ABSTRACT

Based on a reported cluster of multiple sclerosis (MS) cases among people who spent their childhood in the Kern Place-Mission Hills area of El Paso during the 1940s through 1960s, the Texas Department of Health (TDH) under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR) released a public health consultation in 1996 which addressed the possible excess of MS among children who resided in the Kern Place-Mission Hills neighborhoods. The health consultation also addressed environmental concerns centered on past operations at the ASARCO facility, a local metals smelter which had operated in El Paso since 1887 processing primarily lead, copper, cadmium, and zinc. Historically, high levels of metals have been documented from the ASARCO facility's air emissions.

The health consultation recommended a prevalence study of MS among persons who lived in two communities during the 1940s, 1950s, and 1960s; the Kern Place-Mission Hills neighborhood and Smeltertown. Smeltertown was a community of residences owned by ASARCO and located on the company's property. In contrast to the predominately non-Hispanic white and affluent Kern Place-Mission Hills neighborhood, Smeltertown was predominantly Hispanic and poor. Each neighborhood was served by one local public school; the Mesita Elementary school in the Kern Place-Mission Hills neighborhood and the E.B. Jones Elementary school in Smeltertown. TDH applied for and received a competitive grant from ATSDR to examine the prevalence of MS in the cohort of children who lived in the two communities and attended the two public elementary schools. Attendance at the schools was used as a surrogate for living in

the neighborhoods. Funding for the investigation was received in 1997.

A retrospective cohort design was used to investigate the prevalence of MS among the two elementary school cohorts. Students who attended Mesita or E.B. Jones Elementary schools at any time from 1948 through 1970 were eligible for inclusion in the study. The cohorts were identified primarily through school district records, with school record information used to trace cohort members and obtain current addresses. Self-administered mail questionnaires were used to solicit demographic and medical diagnosis information. Medical records of self-reported MS cases were reviewed by a board-certified neurologist to verify diagnosis.

Fourteen cases of definite and probable MS were identified in the Mesita cohort; no cases were reported for the E.B. Jones cohort. The crude MS prevalence estimate for the combined cohort (Mesita and E.B. Jones cohorts combined) was 266 per 100,000. For the Mesita cohort, the crude prevalence estimate was 360 per 100,000. The crude prevalence estimates for both the combined cohort and the Mesita cohort are higher than previously published U.S. prevalence estimates for MS.

Standardized morbidity ratios (SMRs) were also calculated for the combined Mesita and E.B. Jones cohorts and for the Mesita cohort separately. Using data from the 1989-1994 National Institute of Health Survey (NHIS), the SMR for the combined cohort was 1.42 (95% CI = 0.78 - 2.40) indicating an elevated, but not statistically significant risk of MS among the combined cohort. For the Mesita cohort, the SMR was 1.93 (95% CI = 1.06 - 3.24) indicating a statistically significant two-fold increased risk of MS.

In addition to obtaining MS prevalence estimates for the study cohorts, one of the study objectives was to evaluate the feasibility of obtaining historic environmental and biological sampling data from the early 1970s to help address environmental concerns. The environmental and biologic data located during the study demonstrates the potential for study cohort members to have been exposed to heavy metals during their pre-adolescence years. Blood lead surveys conducted by the local health department and the U.S. Centers for Disease Control and Prevention in the early 1970s indicate many children living in the study neighborhoods were exposed to harmful levels of lead. The source of the lead was attributed to the ASARCO smelter. Hair samples from three of the study participants (ponytails from the late 1950s and early 1960s) showed elevated levels of several heavy metals. The source of the metals found in the hair samples cannot be determined with certainty.

The twofold excess risk in the Mesita cohort based on the 1989-1994 NHIS comparison data is most likely a minimum estimate of the true disease burden in the cohort. The lack of appropriate comparison prevalence estimates for Texas precludes a more precise estimate. Current prevalence estimates are needed at the state or regional level to address both etiological issues regarding MS and to also address community concerns as they arise. With limited public health resources, the ability to evaluate purported clusters based on scientifically accurate data is essential both to conserve limited resources and to ensure resources are directed toward those studies which may yield etiologic insight to the disease.

Based on the findings of this study, we recommend four activities. First, to conduct an annual survey of the Mesita and E.B. Jones cohorts for a minimum of two additional years to determine if any additional cases of MS are diagnosed. Second, to develop current MS prevalence estimates for Texas using a standardized case definition and case ascertainment protocol. Third, re-analyze the El Paso MS cluster data when Texas prevalence estimates become available. Fourth, to conduct a national multi-site case control study to examine

metals exposure as an etiologic risk factor for MS and to include participants in the El Paso study if feasible.

EL PASO MULTIPLE SCLEROSIS CLUSTER INVESTIGATION
EL PASO, EL PASO COUNTY, TEXAS

INTRODUCTION

In December 1994, a 42 year-old former El Paso, Texas resident with multiple sclerosis (MS) contacted the Texas Department of Health (TDH) to report an apparent "cluster" of MS cases among people who spent their childhood in the Kern Place-Mission Hills area of El Paso (Appendix A). Based on initial referrals, 15 adults (ages 42 to 53) with MS who resided in the neighborhood as children during the 1940s through 1960s were identified by TDH. Fourteen of the 15 people attended Mesita Elementary School, a neighborhood public school; one person had attended a nearby private school.

Twelve of the former Mesita Elementary school students reported a diagnosis of definite MS by a neurologist; two reported a diagnosis of probable MS. Applying a national prevalence estimate of 102/100,000 to the estimated 3,100 students who attended the Mesita school from 1948 to 1970, approximately three cases of MS would have been expected among the Mesita cohort.[1] During the 1950s and 1960s the Kern Place-Mission Hills area of El Paso consisted of upper income residents and was considered to be one of the more affluent areas of El Paso. In contrast to the remainder of El Paso, the population of these neighborhoods was predominantly non-Hispanic white.

Early in the investigation, concerns were raised by former Mesita students about the possible impact of a local metals smelter, particularly past operations at the facility. Mesita Elementary School is located approximately one mile east-northeast of the American Smelting and Refining Company (ASARCO). The smelter had operated in El Paso since 1887 and had processed primarily lead, copper, cadmium, and zinc. Historically, high levels of metals have been documented from the ASARCO facility's air emissions.[2]

During the 1950s and 1960s the elementary school and residences closest to the smelter were in a community known as Smeltertown (Appendix A). Smeltertown was located on ASARCO property just west of the smelter and separated from the smelter by a single rail track rail line and Paisano Drive (Hwy. 85). In contrast to the Kern Place-Mission Hills neighborhood, the majority of Smeltertown residents were Hispanic and the neighborhood was considered one of the less affluent areas of El Paso. Due to extremely high levels of heavy metals contamination, Smeltertown's only elementary school, E.B. Jones Elementary school, was closed in the early 1970s and the entire community evacuated and the buildings razed in the mid-1970s.[2] No cases of MS were initially reported among former E.B. Jones students.

TDH under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR) released a health consultation in 1996 which addressed the possible excess of MS among children who resided in the Kern Place-Mission Hills neighborhood and related environmental concerns.[2] The health consultation recommended a prevalence study of MS among persons who attended Mesita and E.B. Jones elementary schools. TDH applied for and received a competitive grant from ATSDR to examine the prevalence of MS in the cohort of former Mesita Elementary School students and to determine if the prevalence was elevated compared to national estimates. TDH proposed including former E.B. Jones students in the study, if information was available to enumerate the cohort. Funding for the investigation was received in 1997.

OBJECTIVES

The primary objectives of this study were as follows:

- to conduct a retrospective cohort study to determine if former Mesita students had an increased prevalence of MS as compared with national prevalence estimates.
- to evaluate the feasibility of expanding the study cohort to include former E.B. Jones Elementary School students.
- To evaluate the feasibility of obtaining historic environmental and biological sampling data and matching the data with study cohort members.

BACKGROUND

Multiple Sclerosis

Epidemiology

Multiple sclerosis is one of the most common diseases of the central nervous system.[3] It is characterized by chronic inflammation, demyelination, and gliosis (scarring) of the central nervous system.[4] During the disease process, the myelin sheath which surrounds and insulates nerves is destroyed (demyelination) leaving behind plaques or lesions which appear as hardened scars.[3] The plaques or scars may occur in any area of the central nervous system including the brain and spinal cord. The term multiple sclerosis literally means "many scars". Excluding trauma, MS is the most frequent cause of neurologic disability in early to middle adulthood and is estimated to affect 250,000 to 350,000 people in the United States.[4, 5]

Multiple sclerosis is generally believed to be an immune-mediated disease that occurs in genetically susceptible individuals.[6] The clinical course of MS may vary from an aggressive form which can cause death within months of diagnosis to an asymptomatic condition which is recognized incidentally at autopsy. Most commonly, the clinical course involves a series of remissions and relapses which may become progressively more severe over time.[7, 8] Multiple sclerosis is not usually a fatal disease, but severe disability and decreased quality of life are common.[8] The economic and emotional costs of MS for the affected individuals, family, and friends can be enormous.

Multiple sclerosis differentially affects women, people in the 30 to 60 year old age group, and Caucasians.[1, 8] Approximately twice as many women are affected by MS than men.[4, 9] Multiple sclerosis can be diagnosed at any age, but the age of disease onset typically ranges from 10 to 59 years with the incidence rising steadily from the teens to age 35 and declining gradually thereafter.[4, 8] Men usually have a slightly later age of onset than women.[4] The highest prevalence estimates of MS are seen in people between the ages of 30 and 60.[10] Caucasians of northern and central European ancestry, particularly people of Scandinavian descent, are at highest risk of developing MS, although people of all races and ethnicities may be affected.[8,11]

National prevalence estimates vary widely and are dependent on the methodology and population sample used for the estimate. The most commonly cited U.S. Prevalence estimates come from two national surveys. Baum and Rothschild in 1981 reported a prevalence of 58 per 100,000 population based on a 1976 survey

of physicians and hospitals by the National Institute of Neurological Disorders and Stroke (NINDS).[10] Anderson et al. in 1992 attempted to adjust the 1976 survey data to reflect changes in the U.S. population and improved diagnostic techniques.[5] Anderson et al.'s adjusted prevalence estimate was 95 per 100,000 for the United States.[5] The National Health Interview Survey (NHIS), based on self-reports of MS for 1985 through 1989, provided a prevalence estimate of 102 per 100,000.[1] More recent MS prevalence estimates from the 1989-1994 NHIS surveys indicated a crude prevalence estimate of 87 per 100,000 for the United States.[12] The highest reported estimate for a specific geographic area in the United States is for Olmsted County in Minnesota. The 1985 prevalence estimate for Olmsted County using the centralized diagnostic index at the Mayo Clinic is 160 per 100,000.[13]

Epidemiologic studies have noted the prevalence of MS is not distributed evenly among the world's population.[6,14] In general, the prevalence of MS varies with latitude. In the Northern and Southern Hemispheres, disease estimates increase with increasing latitude with a north-south prevalence gradient demonstrated for Europe, the United States, Japan, Australia, and New Zealand.[11] There are exceptions to the risk gradient in many areas of the world, however, and prevalence can vary among populations living in the same latitude.[15]

Research conducted in the United States has supported the general association between latitude and risk of MS. Both the 1976 NINDS survey and the NHIS surveys have demonstrated the variance in MS prevalence estimates by region in the United States.[1,10] Baum and Rothschild reported the U.S. Prevalence estimate above the 37th parallel as 68.8 per 100,000 and the prevalence estimate below the 37th parallel as 35.5 per 100,000.[10] Using the 1985-1989 NHIS data, the highest prevalence estimate (158 per 100,000) is reported for the midwest region and the lowest prevalence estimates for the southern and western regions (77 per 100,000 and 74 per 100,000).[1]

The most recent study to address the geographic variation in MS incidence in the United States was conducted by Hernan et al. using data from the Nurses' Health Study I and II.[16] Their data confirmed an association between latitude and risk of MS in the United States, but the authors noted there was an attenuation of the north-south gradient over time.

The 1989-1994 NHIS data also demonstrated the variance in MS prevalence estimates among regions in the United States.[12] The prevalence estimates for both males and females in the southern United States are substantially lower than for the rest of the country; statistically lower for females. The female MS prevalence estimate for the southern region is 91 per 100,000; for males it is 36 per 100,000. The southern region of the United States in the NHIS study is a large geographic area which encompasses 15 other states, including Texas, and the District of Columbia. The other states included in the southern region are Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Virginia, and West Virginia. The female prevalence estimates for the northeastern, midwestern, and western regions of the United States ranged from 138 to 141 per 100,000. For males the prevalence estimates ranged from 52 to 56 per 100,000.

Several researchers have suggested the north-south risk gradient in the northern hemisphere may be due, at least in part, to genetic differences in the populations.[11,15] In both the United States and Europe, the

prevalence of MS is closely correlated with the degree of Scandinavian and northern European heritage in the population.[11,14] The ancestry of a given population has been estimated to explain up to 60% of the north-south gradient in the United States.[11] Other explanations for the north-south gradient in the northern hemisphere have included socioeconomic factors, access to medical care, targeted surveillance activities, or the presence of protective environmental factors in certain geographic areas.[11]

Etiology

Although the etiology of MS is unknown, both genetic and environmental theories have been proposed. Hogancamp et al. summarized the evidence which supports the genetic susceptibility theory in four observations: (1) MS is primarily a disease of Caucasians and among Caucasians selected ethnic groups are more vulnerable to MS than others; (2) MS is 20 to 40 times more common in relatives of MS cases than in the general population and shared environmental factors do not appear to account for this increased risk; (3) monozygotic twins (identical twins derived from a single egg) have a concordance rate for MS six times higher than in dizygotic twins (fraternal twins derived from two eggs); and (4) MS is strongly associated with a specific genetic marker, the HLA-DR2 allele.[6,11] Noseworthey et al. noted there is some evidence that the severity and course of MS may also be influenced by genetic factors.[6]

According to Hogancamp et al., the environmental theory suggests MS is a place-related, acquired disease.[11] Some of the evidence cited by Hogancamp et al. and others in support of the environmental theory include: (1) the prevalence of MS varies with geography around the world with the prevalence of MS generally increasing with distance from the equator; (2) limited studies suggest migration may alter the risk of MS and the effect on risk may depend on age at migration; (3) children of immigrants may have prevalence estimates similar to those in their adopted country and different from their places of origin; (4) the concordance rate for MS in monozygotic twins is less than the 100% that might be theoretically expected if the cause of MS was purely genetic; (5) epidemics and clusters of MS have been reported which might suggest the possibility of a single, common source of exposure; and (6) in some areas the incidence of MS has changed faster than could be attributed solely to genetic factors.[6,11]

In a review of migration studies, Kurtzke concluded that migrants from high risk MS areas to lower risk areas retain the risk from their birth place only if they are at least 15 years of age at the time of migration.[17] Studies examining the MS risk of migrants from low risk areas to high MS risk areas suggest that people who migrate in childhood or at an older age increase their risk of developing MS.[18] Kurtzke concluded that data from migrant studies support the idea that MS is ordinarily acquired in early adolescence with a lengthy latent period between disease onset and symptom onset.[17]

Most researchers agree that MS is a disease with multifactorial etiology and that both genetic susceptibility and environmental influences are important determinants in the acquisition and clinical expression of MS.[6,11,19,20]

Environmental Exposures and Multiple Sclerosis

Although the etiology of MS is unknown, a number of environmental exposures have been investigated as possible etiologic factors for MS including infectious agents, solvents, trauma, pets, and diet, but with no

consistent findings.[1,14,20,21] One current theory is that one or more environmental exposures in a genetically susceptible individual may trigger the development of MS.[19,20] Some studies suggest that the critical time period for environmental exposures is prior to puberty.[8,11,15,17,18]

Exposure to metals has also been considered as an etiologic factor in several studies, including cluster investigations. At the onset of this study, the primary environmental concerns shared by study participants were related to the smelting facility and potential childhood exposures to metals and sulfuric acid emissions. Limited information is available from ecologic and occupational studies and cluster investigations regarding exposure to metals and subsequent risk of MS.

Finnish researchers observed a correlation between the distribution of acidic soils, particularly the presence of acid raised bogs in Europe, and MS prevalence.[22] Comparing two Finnish administrative districts with very different MS prevalence estimates, the district with high MS prevalence estimates had much higher soil levels of zinc, aluminum, iron, and chromium than soils in the district with low MS prevalence estimates. Lead and copper soil concentrations were not significantly different between the districts.[22] An MS cluster investigation in Henribourg, Saskatchewan, a Canadian township, also showed higher levels of zinc, lead, chromium, nickel, and calcium in the soil, compared to an area of Saskatchewan where the incidence of MS was very low.[23]

Lauer and Firnhaber examined occupation during adolescence as a possible risk factor for MS at the teaching hospital in Darmstadt, West Germany.[24] Using varying time periods from 1937 through 1970, they compared the occupational histories (prior to age 20) of MS patients with occupational data for the general population. Of 101 male patients, 26% worked in the metal processing trades during adolescence, compared to 17% of the general male population (p<0.01). Lauer and Firnhaber also noted a predominance of pipe-fitters (47% observed vs. 32% expected) among patients who had been metal workers during adolescence. Of the 205 female patients participating in the study, there was a significant preponderance of occupations in commerce and administration (48% versus 32%, p<0.001).[24]

Investigators observed a significantly elevated incidence of MS among individuals who worked in a battery factory in Rochester, New York during 1970 through 1989. Twenty cases of MS among employees were documented over the two decades. The factory used large amounts of zinc as a raw material and employed between 4,446 and 6,626 people during the study period. A trend toward higher serum zinc levels was observed in a sample of workers who worked at the factory from 1970 through 1979 compared with controls not employed at the plant.[25,26]

Eastman et al. reported an apparent cluster of MS cases in Mansfield, Massachusetts in 1973.[27] Fourteen cases of multiple sclerosis were documented in a population of 9,939 for a prevalence estimates two to three times higher than the MS prevalence for the northern United States Eight cases lived within a few blocks of each other in the center of town during their childhoods on a pond highly contaminated with sewage which served as the town's water supply. Eastman et al. speculated about the role of the water supply, either a toxic or infectious agent in the water, in the etiology of MS in the community.[27] Ingalls in a later review of the data noted that the Mansfield Iron Foundry was situated in the center of town and speculated on the role of metals exposure from the foundry as a possible etiologic factor.[28]

A cluster of six MS cases was reported in Mossyrock, Washington (1970 population 415) by Koch in 1974.[29] The estimated prevalence estimate for Mossyrock was 20 times higher than for the state of Washington. The six cases included two sets of siblings (three in one family and two in a second family) and the sixth case was a first cousin of one of the sibling sets. All were childhood playmates. In approximately 1930, when all six individuals were between the ages of 14 and 18, the older brother of one of the cases began a business that involved melting cinnabar on a woodstove in the family barn to recover elemental mercury. He collected the mercury in pans and then poured it into flasks in the presence of his younger siblings, cousins, and, presumably, their friends.[28]

The U.S. Centers for Disease Control and Prevention (CDC) and the Florida Department of Health (FDOH) examined an apparent MS cluster in Key West, Florida in 1985.[30] Early reports of the cluster had focused on a local city dump which had lead and mercury detected in the effluent from the site and which caught fire every few days. Old navy yards in Key West had used antifouling paints containing copper and mercury and there was speculation that some of these paints had been deposited in the landfill.[28] The CDC and FDOH identified 32 cases of definite or probable MS cases and initiated a case-control study to identify possible etiologic factors.[30] The results of the study indicated the MS cases were more likely than population-based controls to have lived longer in Key West, been a nurse, ever visited a local military base, owned a Siamese cat, and had detectable antibodies to two viruses.[30]

In a less studied cluster of 35 prevalent cases of self-reported MS in Galion, Ohio, the Ohio EPA found that the river running through Galion had high levels of cadmium, chromium, and copper after receiving the effluent of local industries. [31] It was not reported whether water, soil, or air were analyzed for other metals.

The most recent cluster investigation report available for review was commissioned by the Whiteside County Health Department to examine the prevalence of MS in Morrison, Illinois.[32] Although the age and sex distribution of Morrison is similar to that of the United States, the population is predominantly white with 83% of the population reporting a northern European heritage. The local chapter of the MS Society conducted case finding. Twenty-nine people self-reported an MS diagnosis. Twenty-two people lived within the Morrison zip code and were included in the prevalence estimate. Based on the 22 self-reported cases the prevalence estimate was 290.5 per 100,000 population for Morrison. The report did not provide information on what prompted the study or any potential etiologic hypotheses.

Site History

The Kern Place-Mission Hills area and Smeltertown are the geographic areas of interest for this study. The Kern Place-Mission Hills area was selected because the initial reported MS cases lived in the area as children. Smeltertown was selected because of its physical location immediately adjacent to the ASARCO facility and because the blood lead studies conducted during the 1970s indicated the most heavily exposed children lived there. [33] The data do not exist which would allow us to reconstruct a complete census of children residing in the neighborhoods. Attendance at the two public elementary schools which served the neighborhoods was used as a surrogate for residence in the neighborhoods.

During the 1950s and 1960s the Kern Place-Mission Hills area of El Paso was comprised of upper income residents and was considered to be one of the more affluent areas of El Paso. The population was

predominantly white and non-Hispanic.[2] The Mesita School, which served the neighborhood, is located approximately one mile east-northeast of the ASARCO facility (Appendix A). The closest residences to the smelter during the 1950s and 1960s were in Smeltertown, which was located immediately west of the smelter on a narrow strip of land owned by ASARCO between the industrial plant and the Rio Grande. Smeltertown was a settlement of houses occupied by smelter workers. Although the neighborhood was eventually supplied with city water, some electricity, and gas; it never had city sewage disposal or drainage for wash water. Ninety-eight percent of the residents of Smeltertown were Hispanic.[2] Smeltertown's only elementary school, E.B. Jones Elementary School, was closed in the early 1970s. Due to extremely high levels of heavy metals contamination the entire community was evacuated in 1972 and the buildings razed in the mid-1970s.[34]

The ASARCO smelter began operations in 1887. Lead smelting was the primary activity at the smelter until approximately 1911 when copper smelting was initiated. The facility became one of the world's largest copper smelters and continued to operate primarily as a copper smelter until 1998. Lead smelting was discontinued in 1985. The smelter had a secondary zinc fuming operation from 1948 until 1982.[35] A smaller cadmium roasting operation also was conducted on an intermittent basis beginning in the 1950s.[36,37] Operations at the smelter were suspended in 1999 and the plant was placed on care and maintenance status.[35]

High levels of metals and sulfur dioxide (SO_2) emissions from the smelter stacks have been well-documented since at least the late 1960s through the 1970s and investigations by health agencies near the smelter in the early 1970s documented extremely high blood lead levels in area residents. [38-40] Extensive environmental sampling in the surrounding communities has also documented elevated levels of lead, zinc, arsenic, cadmium, and SO_2 in many areas of El Paso.[38-40] Detailed information regarding historical environmental data is located in the attached addendum, "Biological and Environmental Sampling Data".

The topography and climate of El Paso create conditions likely to result in high levels of exposure to contaminants in air, soil, and dust. The city is surrounded to the north, northwest, and west by high mountains.[33] Rainfall is sufficient to support only limited vegetation (4 to 10 inches per year) and although winds are moderate (annual average speed is 8.4 miles per hour); a fine, gritty dust often becomes airborne particularly during March and April. Thermal inversions, which can increase exposure to air pollutants, occur on 70% of mornings.[41]

El Paso and ASARCO were the focus of a landmark study examining blood lead levels in the communities in the vicinity of the smelter in 1972.[33] The study examined blood lead levels in a random sample of persons in all age groups living within four miles of the smelter. Results indicated that 53% of children ages one to nine years old living within one mile of the smelter had a blood lead level of 40 micrograms per deciliter of blood (g/dL). In 1972 a blood lead level of 40 g/dl was considered indicative of undue lead absorption.[33] Currently, a blood lead level of 10 g/dl is considered elevated and a level of 20 g/dl would trigger immediate medical intervention.[42] The authors concluded that particulate lead in dust and air accounted for most of the lead exposure in El Paso children and that the smelter was the principal source of the lead.[33]

Three MS patients who attended Mesita Elementary School provided TDH with childhood hair samples for metals analysis as part of the initial investigation. Samples included those cut from the hair of a 12-year-old

girl in 1956, the braid of a 6-year-old girl in 1959, and the ponytail of a 12-year-old girl in 1962. To determine historical exposure levels, TDH had the hair samples analyzed for seven metals by National Medical Services, Inc. in Willow Grove, Pennsylvania. The hair samples from all three girls showed elevated levels of lead and mercury. The hair samples of both 12 year-olds showed elevated zinc and copper levels. In addition, the 1959 hair sample showed an elevated concentration of arsenic and the 1962 sample showed an elevated concentration of cadmium. Additional information regarding the hair samples is located in the attached addendum, "Biological and Environmental Sampling Data."

MATERIALS AND METHODS

Study Overview

A retrospective cohort design was used to investigate the prevalence of MS among two elementary school cohorts. Students who attended Mesita or E.B. Jones Elementary Schools at any time from 1948 through 1970 were eligible for inclusion in the study. The cohorts were identified primarily through school district records, with school record information used to trace cohort members and obtain current addresses. Self-administered mail questionnaires were used to solicit demographic and medical diagnosis information. Medical records of self-reported cases were reviewed by a board-certified neurologist for case status assignment. Prevalence estimates were calculated for the combined study cohort and the Mesita Elementary School and both were compared to national prevalence estimates. The attached addendum contains the historic environmental and biological sampling data collected for Objective 3 of this study.

Cohort Identification

The El Paso Independent School District (EPISD) maintains student records on microfiche dating back to the early 1900s. The microfiche records were reviewed and records of students who attended Mesita and E.B. Jones schools at any time from 1948 through 1970 were retrieved. The1948 through 1970 time period was selected for study based on the expected availability of records, the closing of E.B. Jones in the early 1970s, and the natural history of the disease. Information from Olmsted County, Minnesota indicates the median age at diagnosis for men is 34 years, 32 years for women, and 33 years overall.[13] A student entering either school in 1970 at age 6, would be 36 at the completion of data collection for the study.

Cohort Eligibility

All students enrolled in Mesita or E.B. Jones Elementary Schools at any time in 1948 through 1970, as identified through the EPISD microfiche records or who self-reported attending the schools, were eligible for inclusion in the study cohorts. There was no minimum number of days in attendance required for inclusion in the study cohort.

"Self-reporting" students are those individuals who responded to the TDH survey and reported attending either Mesita or E.B. Jones Elementary Schools during the study period, but for whom we could not match with a school record. The "self-reports" either contacted TDH and specifically asked to be included in the study after hearing about the study through the media or other students or former classmates contacted TDH and asked us to forward the study materials to the person.

Tracing

We attempted to locate current addresses for each former Mesita and E.B. Jones student. The name and address of each student, as listed on the EPISD records, was used to trace members of the school cohorts. The EPISD student records did not have social security numbers recorded for students during 1948 through 1970. Tracing techniques used to locate cohort members included: (1) Internet-based searches using commercial databases; (2) Texas Department of Public Safety drivers' license records; (3) El Paso high schools' alumni associations; (4) a commercial tracing company; (5) TDH Bureau of Vital Statistics; (6) public meetings; (7) the annual reunion of former Smeltertown residents; and (8) referrals from classmates.

Data Collection

A packet of study materials was mailed to all cohort members for whom an address was identified through tracing efforts and referrals from other classmates. The study packet (Appendix B) included an introductory letter, questionnaire, and a form for classmate referrals. All study materials were available in English and Spanish.

The questionnaire solicited basic demographic data, information on school attendance, and MS status. Individuals reporting a diagnosis of MS were contacted by mail and telephone for authorization to review medical records related to their MS diagnosis. A signed medical release of information form (Appendix C) was obtained from each participant prior to requesting medical records. Copies of medical records were reviewed by an independent board-certified neurologist who classified individuals according to case status.

Case Confirmation

The MS case definition used for the study was based on Hauser's criteria as outlined in Harrison's <u>Principles of Internal Medicine</u> (1994).[4] The criteria are as follows:

1. Examination must reveal objective abnormalities of the CNS.

2. Involvement must reflect predominately disease of white matter long tracts, usually including (a) pyramidal pathways, (b) cerebellar pathways, (c) medial longitudinal fasciculus, (d) optic nerve, and (e) posterior columns.

3. Examination or history must implicate involvement of two or more areas of the CNS.

    (a) MRI may be used in patients below the age of 40 to document a second lesion when only one site of abnormality has been demonstrable on examination. A confirmatory MRI must have either four lesions involving the white matter or three lesions if one is periventricular in location. Acceptable lesions must be greater than 3 mm in diameter.

    (b) Evoked response testing may be used to document a second lesion.

4. The clinical pattern must consist of (a) two or more separate episodes of worsening involving different sites of the CNS, each lasting at least 24 hours and occurring at least one month apart or (b) gradual or step-wise progression over at least six months if accompanied by increased CSF IgG synthesis or two or more oligoclonal bands.

5. Age of onset between 15 and 60 years of age.

6. The patient's neurologic condition could not be better attributed to another disease. Laboratory testing that may be advisable in specific cases includes:

> (a) CSF analysis,
>
> (b) MRI of the head or spine,
>
> (c) serum B_{12} level,
>
> (d) human T cell lymphotropic virus type I (HTLV-I) titer,
>
> (e) sedimentation rate,
>
> (f) rheumatoid factor, antinuclear, anti-DNA antibodies (SLE),
>
> (g) serum VDRL,
>
> (h) angiotensin-converting enzyme (sarcoidosis),
>
> (i) *Borrelia* serology (Lyme disease),
>
> (j) very long chain fatty acids (adrenoleukodystrophy), and
>
> (k) serum or CSF lactate, muscle biopsy, or mitochondrial DNA analysis (mitochondrial disorders).

Based on the six criteria listed above, Hauser formed three diagnostic categories:

1. *Definite MS.* All six criteria fulfilled.

2. *Probable MS.* All six criteria fulfilled except only one objective abnormality despite two symptomatic episodes or one symptomatic episode and unrelated signs detected on examination.

3. *At Risk for MS.* All six criteria fulfilled except one symptomatic episode and corresponding signs detected on examination.

Using Hauser's diagnostic categories, the study neurologist classified individuals self-reporting MS into one of four diagnostic categories based on a review of medical records: (1) definite MS, (2) probable MS, (3) at-risk for MS, or (4) not MS.

Data Management and Quality Control

Student Records

The EPISD microfiche records from 1948 through 1970 were reviewed by a contractor to identify former Mesita and E.B. Jones students. The contractor provided TDH with hard copies of the records. Each student was assigned a unique identifier. Pertinent information from the student records was entered into an EpiInfo database to facilitate tracking and tracing activities. Internal consistency and validity programs were used to check for data entry errors and duplicates. Records were also manually checked against the database for duplicates and selected data fields.

Questionnaires

Self-administered mail questionnaires were the primary data collection tool used to gather cohort and case information. Returned questionnaires were reviewed and checked against the tracking database for study eligibility. Questionnaires were also reviewed for completeness and accuracy. EpiInfo was used for data entry of demographic information and case status. Internal consistency and validity programs were used to check

for data entry errors and duplicates.

In those cases when questionnaire information conflicted with information provided on the school records, the information from the school records was used for analysis.

Medical Records

Questionnaire respondents who indicated a diagnosis of MS were contacted by mail and telephone to request written authorization to obtain medical records related to the MS diagnosis. Copies of pertinent medical records were obtained from physicians and hospitals.

Case Confirmation

Dr. Randolph Schiffer, MD, served as the consulting neurologist. Dr. Schiffer reviewed all medical records and classified self-reported cases into one of four diagnostic categories (definite, probable, at-risk, or not MS) based on the case definition used for this study. The case definition was specified prior to data collection. A written summary of the neurologic review was completed for each individual.

Protection of Human Subjects

The TDH study protocol, questionnaire, and study materials were submitted to the CDC Institutional Review Board (IRB) for their review and received approval to proceed with the study in June 1997. In accordance with the Privacy Act of 1974 (5 U.S.C. Section 552a(e) and the Texas Health and Safety Code (Chapter 161, Sections 161.02 and 161.022, which keeps the identity and condition of persons studied confidential), all completed questionnaire forms and other identifying information were kept secure and access was limited to authorized study personnel. The findings of this study are presented in aggregate form to avoid disclosing the identity of any specific study participants.

Data Analysis

Descriptive and analytic procedures were used to describe the study cohorts, determine prevalence estimates for MS, and compare MS prevalence estimates in the study cohorts with published national estimates. Descriptive statistics were used to summarize the demographic characteristics of the study cohort, including the combined cohort and the Mesita and E.B. Jones cohorts separately. Prevalence estimates and comparisons are presented for the combined diagnostic categories of definite and probable cases. The primary data analyses were conducted on the combined cohort and the Mesita cohort.

RESULTS

The following sections summarize the results of the cohort enumeration, participation rates, demographics of the study population, and the estimated prevalence of MS in the study cohort.

Cohort Enumeration

Combined Cohort

A total of 5,272 students were identified as having attended Mesita and E.B. Jones Elementary Schools from 1948 through 1970. The combined cohort included 5,097 students who were identified through EPISD

records and 175 people who self-reported attending either school. All self-reported students were included in the study cohort. It is possible that many of the self-reported students are included among the students with school records, but due to the poor quality of some of the school records and missing or incomplete information on the returned questionnaires, a confirmed match could not be made. Three students in the combined cohort attended both schools during the study time period. They are counted once in the combined cohort counts and separately in each school cohort.

Overall for the combined cohort, there was an equal distribution of males and females, the range of ages was 35 to 69 years (as of June 2000), the mean age was 50.6 years, and the mean number of years in attendance was 3.7. Comparing the self-reported students with the students with school records, there were more females (61%), they were slightly younger (mean age 48 versus 51), and they attended the schools slightly longer (4.5 years versus 3.7 years). Although there were some differences noted between the self-reported cohort members and those with school records, they accounted for a very small portion of the overall cohort (3%) and did not influence the distribution of any demographic characteristic of the cohort. Table 1 provides information on the demographic characteristics of the combined cohort.

Mesita

Using EPISD microfiche records, 3,761 students were identified as having attended Mesita Elementary School from 1948 through 1970. In addition, 130 people self-reported as having attended Mesita during the study period. All self-reported students were included in the cohort listing. Combining the students identified from the EPISD records and self-reports, the total Mesita cohort for the study period was 3,891.

There were slightly more females in the Mesita cohort than males (51% versus 49%). The mean age of the cohort as of June 2000 was 50.4 years with an age range of 35 to 69. The range of years in attendance at Mesita was 1 to 9 years with an average of 3.6 years in attendance.

Table 1 provides information on the demographic characteristics of the Mesita cohort.

Yearbooks for Mesita Elementary were available for the school years 1957 through 1966. For the 130 students who self-reported attendance at Mesita during the study period, 104 reported attendance during the school years covered by the yearbooks. We were able to confirm 63 of the 104 (61%) as having attended Mesita using the yearbooks. It is possible that more of the 104 students are actually listed in the yearbook, but due to the use of nicknames in the yearbook and spelling inconsistencies between the yearbook and questionnaires, we could not confirm a match.

We also checked the students listed in the 1957 yearbook against the school records we received from EPISD to assess the completeness of the Mesita records. Ninety-two percent of the students listed in the yearbook were found in the school records used in this study. The 92% should be taken as a conservative estimate, however. Due to the use of nicknames in the yearbook and spelling inconsistencies, we could not confirm a match for all students in the yearbook with available school records.

E.B. Jones

The EPISD microfiche records identified 1,339 former E.B. Jones students. Forty-five individuals self-reported as having attended the school during the study period. No yearbooks were available to confirm attendance. Combining the students identified through EPISD records and self-reports, the total number of

students in the E.B. Jones cohort was 1,384.

The demographic characteristics of the E.B. Jones cohort was somewhat different from the Mesita cohort. There were more males than females in the Jones cohort (52% versus 48%) and the mean age was slightly older at 51.1 years. The average number of years at the school was very similar at 3.9 years.

Tracing and Participation Rates

Using the tracing procedures described previously, successful traces were completed for 33% (n=1,248) of former Mesita students and 32% (n=432) of former E.B. Jones students. For the combined cohort, successful traces were completed for 33% of the former students. A successful trace was defined as obtaining a current address or confirming the death of a former student for whom student records were available to confirm attendance at either E.B. Jones or Mesita. Sixty-three individuals were confirmed as having died in the study cohort; 57 in the Mesita cohort and six in the E.B. Jones cohort. The vital status of the 63 individuals was ascertained from school records, notification by family members or friends, and through a search of Texas death certificates.

Participation rates for the portion of the Mesita and E.B. Jones cohorts which were successfully traced from the school records are 44% (n=547) and 20% (n=86), respectively. Participation was defined as the return of a completed mail questionnaire or confirmation of vital status. These percentages do not include those former students who self-reported. Some of the self-reported students may have been included in the portion of the cohort which was successfully traced, but due to lack of information or incomplete information (full name, maiden name, and birth date) on the returned questionnaire we could not confirm a match with the returned questionnaire and a student record.

For the combined cohort (n=5,272), 16% of the former students returned a questionnaire or were confirmed as deceased. This includes the 625 individuals who were traced and returned surveys and the 175 former students who self-reported. For the Mesita and E.B. Jones cohorts, 19% and 10% of the former students returned questionnaires or were confirmed as deceased.

Demographics of Study Participants

Table 2 contains a summary of the demographic information available for study participants in the combined cohort and the Mesita and E.B. Jones cohorts including sex, race/ethnicity, age, years in school, and current residence. The summary information for the combined cohort is strongly influenced by the large proportion of Mesita respondents. Three variables were available which would allow a comparison of the respondents with that of the entire cohort; sex, age, and years in school.

Combined Cohort

Overall, for the combined cohort respondents, of those returning questionnaires, a larger percentage were women (55%). For the entire combined cohort, the distribution of males and females was 50% each (Table 1). Seventy-three percent of the respondents were non-Hispanic white. The age range (35 to 69 years) and the mean age (51 years) of the respondents were the same as that of the entire combined cohort. The respondents reported an average of 5.0 years in one of the schools versus the 3.7 years as reported from school records for the entire combined cohort. Almost half of the respondents (47%) lived in El Paso at the time of the study; 73% still reside in Texas.

Mesita

Of those responding to the survey in the Mesita cohort, 55% were women. For the entire Mesita cohort, the sex distribution was 51% females and 49% males. Eighty-six percent of the respondents were non-Hispanic whites; 10% self-reported as Hispanic. The age range (36 to 69) and the average age (51 years) of the respondents were almost identical to that of the entire cohort. The average number of years at Mesita was higher for respondents than it was for the entire Mesita cohort; 5.1 versus 3.6 years. Seventy-one percent of the respondents still reside in Texas with 42% still in El Paso.

E.B. Jones

The percentage of women and men responding from the E.B. Jones cohort was very similar (51% and 49%). In contrast to the Mesita respondents, 93% of the E.B. Jones participants were Hispanic. The range of ages for the respondents was identical to that of the entire E.B. Jones cohort (35 to 67). The average age of respondents was slightly higher at 53 years than that of the entire cohort at 51 years of age. As in the Mesita cohort, the E.B. Jones respondents reported more years at the school (mean 4.5 years) than the entire cohort (3.9 years). Eighty-four percent of the E.B. Jones respondents still reside in Texas with 75% in El Paso.

MS Cases

No cases of MS were reported for the E.B. Jones cohort. Twenty-two cases of MS in the Mesita cohort were self-reported during this investigation. These included the 15 cases that prompted the study and seven additional ones which were reported as a result of case finding efforts of the study. Of the 22 self-reported cases, the case status for 12 individuals was confirmed as definite MS, two as probable MS, one as at-risk for MS, and two people were classified as not having MS. Two people who initially self-reported an MS diagnosis declined to participate in the medical records review portion of the study and could not be classified as to case status. For one individual, the original diagnostic records were not available to confirm the MS diagnosis, even though recent medical records (including hospital records) note an MS diagnosis. Two of the self-reported cases of MS did not attend either Mesita or E.B. Jones during the study period and were not eligible for inclusion in the study. School records were available for the other 20 reported individuals.

Table 3 summarizes the results of the medical record and case confirmation review for the 22 self-reported cases from the Mesita cohort.

MS Prevalence Estimates

Crude and sex-specific prevalence estimates were calculated for the combined cohort and the Mesita cohort. No estimates were calculated for the E.B. Jones cohort because no cases were reported. Definite and probable MS cases were combined for the numerator. The denominators for the crude estimates were based on the entire combined cohort (n= 5,272) or the entire Mesita cohort (n=3,891). The denominator for the sex-specific estimates was the total number of males in either the combined cohort or the Mesita cohort and the total number of females in either cohort group. Age- and sex-specific estimates were also calculated for the combined and Mesita cohorts and compared with estimates from two studies.

Combined Cohort

Using the 14 definite and probable cases of MS and dividing by the total combined cohort (n=5,272), the

crude MS prevalence estimate for the combined school cohort is 266 per 100,000 (95% CI = 145 to 445 per 100,000). All 14 individuals with definite and probable MS classified their race/ethnicity as non-Hispanic white. A wide range of crude prevalence estimates have been reported in published U.S. Studies Table 4 lists the crude prevalence estimates from selected U.S. Studies The crude prevalence estimate for the combined cohort is higher than any of the reported prevalence estimates.

Sex-specific estimates were calculated for males and females in the combined cohort. There were four cases of MS among males in the combined cohort. Dividing by the total number of males in the cohort (n=2,608), the prevalence estimate is 153 per 100,000 (95% CI = 42 to 392 per 100,000). For females, 10 definite and probable MS cases were confirmed for a estimate of 375 per 100,000 (95% CI = 180 to 689 per 100,000).

Tables 5 and 6 summarize the sex- and age-specific prevalence estimates calculated for the combined cohort and the comparisons of the estimates with the Olmsted County and 1989 to 1994 NHIS data. All of the confirmed cases were between the age of 46 and 59 years (age as of June 30, 2000). Slightly elevated estimates are seen for females in the 45 to 54 age group in the combined cohort compared to the Olmsted County population (Table 5), but are not statistically significantly different. In comparison to the 1989-1994 NHIS age-specific prevalence estimates for the entire United States (Table 6), the prevalence estimate for males in the 51 to 60 age group of the combined cohort is approximately three times the national estimate. For women in the combined cohort, elevated prevalence estimates are seen in both the 41 to 50 and the 51 to 60 age groups. Population information was not available from the NHIS data to allow statistical testing of the difference in prevalence estimates between the NHIS national estimates and the combined cohort.

Mesita

Using the 14 definite and probable cases of MS and dividing by the total Mesita cohort (n=3,891), the crude MS prevalence estimate for the Mesita cohort is 360 per 100,000 (95% CI = 197 to 603 per 100,000). All 14 individuals with definite and probable MS classified their race/ethnicity as non-Hispanic white. As noted above, a wide range of crude prevalence estimates have been reported U.S. published studies as summarized in Table 4. The crude prevalence estimate for the Mesita cohort was two to six times higher than any of the previously published estimates.

Sex-specific prevalence estimates were calculated separately for males and females in the Mesita cohort. There were four cases of MS among males (n=1,896) in the Mesita cohort for a prevalence estimate of 211 per 100,000 (95% CI = 58 to 539 per 100,000). For females (n=1,995), 10 definite and probable MS cases were confirmed for a estimate of 501 per 100,000 (95% CI = 241 to 920 per 100,000).

Tables 7 and 8 summarize the sex- and age-specific prevalence estimates calculated for the Mesita cohort and the comparisons of the estimates with the Olmsted County and 1989-1994 NHIS data. All of the confirmed cases were between the age of 46 and 59 years (age as of June 30, 2000). As compared to the Olmsted County data (Table 7), elevated prevalence estimates are seen for males and females in the 45 to 54 age group and in males in the 55 to 64 age group. In comparison to the 1989-1994 NHIS age-specific prevalence estimates (Table 8), the prevalence estimate for Mesita males in the 51 to 60 age group is four times the national estimate. For women in the combined cohort, elevated prevalence estimates are seen in both the 41 to 50 and the 51 to 60 age groups; almost twice as high in the 41 to 50 age group and two and a half times as high in the 51 to 60 age group.

<u>E.B. Jones</u>

There were no MS cases reported in the E.B. Jones cohort. Prevalence estimates could not be calculated for the cohort..

Standardized Morbidity Ratios (SMRs)

Standardized morbidity ratios (SMR) were also calculated for the combined cohort and the Mesita cohort. Prevalence estimates from three different studies were used to calculate standardized morbidity ratios for the two cohort groups. The SMRs were calculated by applying age-specific prevalence estimates from the three studies to the appropriate age groups in either the combined cohort or the Mesita cohort to generate the expected number of cases for each age category. These age- specific expected numbers were summed to obtain the total expected number of MS cases. The ratio of observed to expected cases was calculated to obtain the SMR. An SMR equal to one indicates that the number of observed MS cases is exactly the number expected based on the Prevalence estimate of MS in a comparison population. An SMR greater than one means more cases were observed than would be expected and an SMR of less than one means fewer cases of MS were observed than what would be expected based on a comparison population. The SMRs were tested for significant deviation from 1.00 by using Fisher's exact test and exact confidence intervals for the Poisson variate. When the 95% confidence interval for the SMR includes 1.00, no statistical excess of disease is indicated.

<u>Combined Cohort</u>

Standardized morbidity ratios (SMRs) were calculated based on the age-specific prevalence estimates from Baum and Rothschild [10], Wynn et al.[13], and the 1989-1994 NHIS survey data.[12] Using the age-specific prevalence estimates from Baum and Rothschild [10], the combined cohort shows a statistically significant twofold excess (SMR=2.05, 95% CI =1.12 - 3.43). Using the Olmsted County data from Wynn et al.[13], however, the SMR is 0.77 (95% CI = 0.42 - 1.30) demonstrating a decreased risk of MS in the combined cohort. Based on the preliminary data from the 1989-1994 NHIS surveys [12], the SMR for the combined cohort is 1.42 (95% CI = 0.78 - 2.40), indicating a non-statistically significant increased risk of MS in the cohort. Table 9 shows the number of expected cases, SMRs, and 95% confidence intervals based on the three different comparisons.

<u>Mesita</u>

SMRs were calculated for the Mesita cohort using the information on age-specific MS prevalence estimates from Baum and Rothschild [10], Wynn et al.[13], and the 1989-1994 NHIS survey[12] and are summarized in Table 10. The SMR calculated using the age-specific prevalence estimates from Baum and Rothschild [10] for the Mesita cohort shows an approximate three-fold excess of MS in the Mesita cohort (SMR=2.80, 95% CI =1.52 - 4.66). The excess is statistically significant. A statistically significant twofold excess is also shown using the NHIS data[12] (SMR= 1.93, 95% CI = 1.06 - 3.24). Using the Olmsted County data [13], essentially no excess of MS is demonstrated in the Mesita cohort.

<u>E.B. Jones</u>

There were no MS cases reported in the E.B. Jones cohort. SMRs could not be calculated for the cohort.

DISCUSSION

We have presented prevalence and risk estimates for the combined school cohort and the Mesita school cohort, based on a wide range of comparison estimates. All of the MS cases were reported for former Mesita students; 14 definite and probable MS cases were confirmed. No cases were reported for the E.B. Jones cohort. Because the prevalence estimates and risk estimates in the combined school cohorts reflect only Mesita cases, this discussion will focus on the information and analyses conducted for the Mesita and E.B. Jones schools separately.

For the Mesita cohort interpreting the results of the study was problematic because current comparison MS prevalence estimates, appropriate for use with the El Paso school cohorts, were not available. Comparison prevalence estimates are used to estimate how many cases of a disease we would expect to find in a population and provide the benchmark against which we measure the excess (or deficit) number of cases in a population. The ideal comparison prevalence estimate would use the same case definition as this study's case definition, cover the same time period as the study, provide sex- and age-specific prevalence estimates, and be state- or region-specific to Texas. If the prevalence of MS in the United States is increasing, as is indicated by the Olmsted County data from the Mayo clinic[13], timely prevalence estimates are of vital importance in evaluating purported clusters.

For this study, the available comparison prevalence estimates did not match any of the criteria listed above for an ideal comparison prevalence estimate. The Baum and Rothschild [10] prevalence estimates, while physician diagnosed and collected at multiple sites around the United States, are based on data collected over 25 years ago and may not be reflective of the current prevalence of MS in the United States or in Texas. The Mayo Clinic data [13] were collected in one select geographic location in an area of known high prevalence and are apparently not reflective of the MS prevalence experience of the United States or Texas, based on the limited regional data available for comparison. The Mayo Clinic data is physician diagnosed, but it is also over a decade old. The 1989-1994 NHIS [12] data is based on a national survey and should be the most representative data available for the United States. It is also the most current data available. The primary shortcoming of the NHIS data, however, is that it is based on self-reports of MS, not medically confirmed cases. In the absence of good comparison estimates, we presented comparisons based on a range of prevalence estimates found in different studies and surveys. Depending on the comparison prevalence estimate used, there is a considerable difference in the resulting risk estimate for the Mesita cohort.

For the final analysis and interpretation of the Mesita cohort findings we chose to use the 1989-1994 NHIS data.[12] The 1989-1994 NHIS data set is the most recently available and should be more reflective of the current age structure and overall prevalence experience of the United States than the other available prevalence estimates. Using the NHIS data as a comparison, a statistically significant twofold excess of MS in the Mesita cohort was evident after adjustment for age (SMR = 1.93, 95% CI 1.06 - 3.24). This excess was demonstrated in less than 20% of the total Mesita cohort (33% of the cohort was successfully traced, 44% of those traced responded to the questionnaire). The twofold excess demonstrated for the cohort should be considered a minimum estimate of the disease burden in the Mesita cohort for two reasons.

First, if there is a regional gradient of risk in the United States as is indicated by the 1989-1994 NHIS data and other studies, El Paso would be in one of the lower prevalence regions and the NHIS data would overestimate the expected number of cases in the cohort. This is illustrated by the sex-specific prevalence

estimates reported for the southern region of the United States in the 1989-1994 NHIS data.[12] The NHIS data estimate an overall MS prevalence for U.S. males at 48 per 100,000 and for females at 123 per 100,000. The NHIS regional data for the southern region of the United States which includes Texas, estimate an MS prevalence for females at 91 per 100,000 and for males at 36 per 100,000. For the Mesita cohort, the prevalence estimate for females was 501 per 100,000 and for males the prevalence estimate was 211 per 100,000. If prevalence estimates for the region were available which used physician-confirmed cases of MS instead of self-reported cases, the expected number of MS cases could be further reduced resulting in an increased risk estimate.

Second, the 14 definite and probable cases used in the Mesita risk estimates do not represent all of the cases of MS in the cohort. One participant in this study has been treated by several physicians for MS. We were not able to include this person in our case count, however, because the medical records containing information on his original diagnosis could not be located for review and we could not classify the person according to the criteria in our case definition. We also have one person classified in the at-risk category and two people who self-reported MS, but have declined to participate in the case confirmation portion of the study. These four people would have been counted as cases of MS under the case definition used in 1989-1994 NHIS survey.[12] It is also reasonable to assume there may be additional MS cases in the 67% of the Mesita cohort we were unable to locate during the course of the study.

With the assistance of the EPISD we were able to access records for the former E.B. Jones students and include them in the study. We were able to identify current addresses for 32% of the cohort; 20% of those for whom we obtained address returned a questionnaire. No cases of MS were reported among the 125 people who responded to our survey.

The twofold excess of MS demonstrated for the Mesita cohort and the zero cases reported for the E.B. Jones cohort could be due to a true difference in the disease experience of the two cohorts or could be due to the lack of participation and reporting by the former E.B. Jones students. The difference in the participation rates between the two cohorts may be attributed to a variety of factors. Although TDH outreach efforts were similar for both cohorts, we were not able to identify a strong community advocate from the E.B. Jones cohort until very late in the study. The original MS cases were reported for the Mesita cohort and we received sustained and active support for the study from several individuals in the Mesita cohort. Issues of access to medical care in the United States, the availability of health care in Mexico, and the ability of people to pursue a difficult diagnosis for a disease like MS may also be issues which could affect the number of recognized MS cases in the E.B. Jones cohort, the participation rate, and reporting of a diagnosis of MS.

A lack of trust in government and the lack of perceived benefit for the community may also have been a contributing factor in the low participation rate for the E.B. Jones cohort. Many members of the E.B. Jones cohort were either part of the childhood lead studies conducted in the early 1970s or had family or friends who participated. Several people from E.B. Jones raised the issue of the blood lead studies and noted their concerns about being used as study subjects again. Issues were also raised regarding environmental conditions in 1948 through 1970 and the perceived lack of government response to those conditions.

This study illustrates the need for timely and state- or regional-specific MS prevalence estimates for use in cluster investigations. The confirmation of an excess of disease is the first step in any investigation of a cluster. The estimate of excess disease burden in a population may also drive the decision to pursue an etiologic study of the cluster. A wide range of prevalence estimates, particularly dated prevalence estimates for a disease

with increasing prevalence, may result in erroneous findings. Depending on the comparison prevalence estimate used to evaluate the Mesita cohort cases, we could have reported no excess of MS in the Mesita cohort (SMR = 1.05) up to a threefold excess (SMR = 2.80). Particularly with limited public health resources, the ability to evaluate purported clusters based on scientifically accurate data is essential both to conserve limited resources and to ensure resources are directed toward those studies which may yield etiologic insight to the disease.

Study Strengths and Limitations

This study had a number of strengths which are typically lacking in cluster investigations, particularly MS cluster investigations. We used a retrospective cohort design which allowed us to define our population temporally and spatially prior to disease onset or knowledge of the disease and during pre-adolescence, the purported period of critical susceptibility. We used a standard case definition and diagnostic criteria which were specified prior to the initiation of the study activities. Cases were confirmed by an independent neurologist, not connected to any of the cases, based on medical record review. For the portion of the cohort which chose to participate in the study, we believe we have fairly complete case ascertainment, even though not all of the cases agreed to participate in the case confirmation portion of the study. We have also received excellent support for this study from those individuals who have been diagnosed with MS and from other interested portions of the cohort.

The primary limitation of this study is the lack of appropriate MS comparison prevalence estimates for Texas or for the southwest region of the United States Although an excess of MS is evident in the Mesita cohort, the lack of appropriate comparison prevalence estimates precludes an assessment of the true impact of the disease in the cohort.

Other important limitations of this study are related to our inability to trace approximately 70% of both the Mesita and E.B. Jones cohorts. During our study period, children were not required to have social security numbers. Most successful tracing strategies today use social security numbers as the primary identifier. Given financial and time constraints, the lack of social security numbers severely limited our tracing options and success. The lack of social security numbers may have been particularly limiting in our ability to locate anyone who had changed their name, including women who had married and adopted their husband's last name. For the individuals who were successfully traced (a current address was located), we had a 44% participation rate for the Mesita cohort and a 20% participation rate for the E.B. Jones cohort.

The delay from the time the initial cluster was reported to TDH to the time the study was funded and initiated may have negatively affected both our tracing activities and cohort response rates. During the three year interim between the cluster report and the receipt of funds for the study, six TDH epidemiologists had contact with community and the EPISD. The change in TDH staff and the delay in starting the study lead to a loss of momentum and continuity with community, school district, and local governmental contacts.

The demolition of Smeltertown and subsequent dispersal of the residents may have also played a role in our low percentage of successful traces and the response rate from former E.B. Jones students. Additional time and resources may have improved community outreach efforts and facilitated additional contacts. Within the scope of this study, we were not able to access one potentially very important source of information for the E.B. Jones cohort which also may have facilitated tracing, worker records from the smelter which employed the people who lived in Smeltertown. Access to worker records was requested, but declined by ASARCO.

The delay in initiating the cohort study has also resulted in a loss of participation of several of the original people who self-reported an MS diagnosis. Reasons for non-participation have included fear of disclosure of disease status, progressive illness, and death. We were unable to retrieve medical records on one MS case who had originally been diagnosed in the 1980s. Although subsequent medical evaluations noted a diagnosis of MS on medical records, the original diagnostic information necessary for case confirmation in this study could not be located.

Use of the school records as surrogate listings for the children who grew up in the study neighborhoods also precludes us from addressing the true risk of MS in children who lived in the neighborhoods early in life. We have information on several individuals who lived in the study neighborhoods as children and have subsequently developed MS, but who attended private school and were not eligible for inclusion in this study.

Limited community awareness of the seriousness of the disease may have also affected the study results. Multiple sclerosis is not a familiar diagnosis for most of the general public. Compared to studies of birth defects or cancer, the MS investigation has generated far less publicity and attracted far less community attention. Even a large public meeting in El Paso generated a lower level of concern than is usually associated with a serious disease connected with environmental concerns.

CONCLUSIONS

Based on less than 20% of the enumerated Mesita Elementary School cohort, we found a statistically significant twofold excess of MS based on 14 cases of definite and probable MS. No cases of MS were reported for the E.B. Jones cohort, but less than 10% (n=125) of the cohort was located and participated in the study. The age of the school records used to identify cohort members and particularly the lack of social security numbers severely limited our ability to locate former Mesita and E.B. Jones students.

The twofold excess risk in the Mesita cohort is most likely a minimum estimate of the true disease burden in the cohort. The lack of appropriate comparison prevalence estimates for Texas or for the region precludes a more precise estimate. Current prevalence estimates are needed at the state or regional level to address both etiological issues regarding MS and to also address community concerns as they arise.

We were able to retrieve additional historic environmental and biological sampling data from the early 1970s which demonstrated the potential for cohort members to have been exposed to heavy metals during their preadolescence years while residing in the Mission Hills-Kerns Place and Smeltertown neighborhoods from 1948 through 1970. These data are summarized in the attached Addendum. Blood lead surveys indicate children living in the study neighborhoods in the early 1970s not only had potential exposure opportunity, but were actually exposed to harmful levels of lead. The hair samples from three of our study participants also demonstrate not only exposure potential, but actual exposures to a number of heavy metals, although the source of the exposure cannot be determined with certainty from the hair samples.

The environmental and biological data could not generally be matched to individuals with a high degree of confidence, but could potentially be used to reconstruct general risk estimates based on residence during childhood. The environmental and blood lead data, however, were collected after the study period and not during the time period of primary concern.

This study was designed to determine the prevalence of MS in the school cohorts and review the available environmental and biologic sampling data, not to examine etiologic risk factors for MS. No conclusions may

be drawn regarding metals exposure in the Mesita cohort and subsequent risk for MS. The results of this study do suggest, however, that metals exposure should be studied as a possible risk factor for MS in future studies.

RECOMMENDATIONS

1. Conduct an annual survey of the Mesita and E.B. Jones cohorts for a minimum of two additional years to determine if any additional cases of MS are diagnosed.

2. Develop current MS prevalence estimates for Texas. Age- and sex-specific prevalence estimates should be developed based on a standardized case definition and case ascertainment protocol.

3. Re-analyze the El Paso MS cluster data when Texas prevalence estimates become available. The true magnitude of the excess in the Mesita cohort cannot be ascertained without appropriate comparison prevalence estimates. Re-evaluate the feasibility of conducting a case-control study using the Mesita cohort.

4. Conduct a national multi-site case control study to examine metals exposure as an etiologic risk factor for MS. Combining MS cases from multiple sites around the United States may provide the statistical power needed to study the association between metals exposure and MS. Nontraditional biological samples, such as childhood hair, should be included in the case-control study. Participants in the El Paso study should be included in the multi-site study.

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TABLES

Table 1. - Demographic characteristics of the combined cohort and Mesita and E.B. Jones Elementary School cohorts.

Source of cohort enumeration:	COMBINED COHORT			MESITA ELEMENTARY			E.B. JONES ELEMENTARY		
	EPISD[1] Microfiche	Self-Reports	Total Cohort[2]	EPISD[1] Microfiche	Self-Reports	Total Cohort	EPISD[1] Microfiche	Self-Reports	Total Cohort
	5,097 (97%)	175 (3%)	5,272	3,761 (97%)	130 (3%)	3,891	1,339 (97%)	45 (3%)	1,384
Sex distribution:									
Male	2,539 (50%)	69 39%)	2,608 (50%)	1,847 (49%)	49 (38%)	1,896 (49%)	694 (52%)	20 (44%)	714 (52%)
Female	2,558 (50%)	106 (61%)	2,664 (50%)	1,914 (51%)	81 (62%)	1,995 (51%)	645 (48%)	25 (56%)	670 (48%)
Age Distribution: [3]									
range of ages	35 - 69	35 - 67	35 - 69	35 - 69	36 - 65	35 - 69	36 - 67	35 - 67	35 - 67
mean age in years (SD)	50.7 (6.1)	47.6 (9.6)	50.6 (6.3)	50.6 (6.2)	45.5 (8.3)	50.4 (6.3)	51.0 (5.9)	53.7 (10.5)	51.1 (6.2)
Years in School: [4]									
range of years	1-10	1-8	1-10	1-9	1-8	1-9	1-10	1-8	1-10
mean number of years (SD)	3.7 (2.5)	4.5 (2.5)	3.7 (2.5)	3.6 (2.5)	4.4 (2.4)	3.6 (2.5)	3.9 (2.4)	4.8 (2.8)	3.9 (2.4)

[1] El Paso Independent School District

[2] three students attended both schools. They are counted once in the combined cohort counts and separately in each school cohort.

[3] age as of June 30, 2000. Date of birth was missing for five students in the combined cohort.

[4] the total number of years in school was missing for eight students in the combined cohort

Table 2. - Demographic characteristics of the combined cohort, Mesita, and E.B. Jones cohort study participants.

	COMBINED COHORT[1]		MESITA ELEMENTARY		E.B. JONES ELEMENTARY	
	Number	Percent	Number	Percent	Number	Percent
Sex distribution:						
Male	362	45%	302	45%	61	49%
Female	438	55%	375	55%	64	51%

Race/Ethnicity:						
Non-Hispanic White	586	73%	584	86%	3	2%
Hispanic	182	23%	67	10%	116	93%
Other/Unknown	32	4%	26	4%	6	5%
Age Distribution: [2]						
range of ages	35 - 69	--	36 - 69	--	35 - 67	--
mean age in years (SD)	51.3 (6.8)	-	51.0 (6.6)	-	52.9 (7.5)	--
Years in School: [3]						
range of years	1 - 9	--	1 - 9	--	1 - 9	--
mean number of years (SD)	5.0 (2.5)	-	5.1 (2.4)	-	4.5 (2.6)	--
Current Residence:						
El Paso	374	47%	282	42%	94	75%
Texas (not El Paso)	204	26%	193	29%	11	9%
Other States	222	28%	202	30%	20	16%
Total Participants:	800[1]		677		125	

[1] two students attended both schools and returned questionnaires. They are counted once in the combined cohort counts and separately in each school cohort.

[2] age as of June 30, 2000. Date of birth was missing for five Mesita students.

[3] the total number of years in school was missing for five Mesita and three E.B. Jones students.

Table 3. - Case status of the 22 self-reported cases of MS from the Mesita cohort.

CASE STATUS	MALE	FEMALE	TOTAL	COMMENTS
Definite	4	8	12	
Probable	0	2	2	
At-risk	0	1	1	
Not MS	0	2	2	Did not meet case definition for MS.
Other	1	0	1	MS diagnosis noted in medical records. Diagnostic criteria unavailable to confirm.
Declined Participation	1	1	2	
Not Eligible	0	2	2	Did not met study eligibility criteria. Did not attend Mesita or Jones during the study period.

Table 4. - MS prevalence estimates from selected U.S. studies. [1]

		Prevalence Estimates	

Authors	Location	Year	Number of Cases	Prevalence estimate/100,000 (95% CI)	Type of Study
NHIS Data 1989 - 1994 (unpublished) (2001)	United States	1989-94	120,000 annually	87	national survey (NHIS[2])
Jacobsen (1996)	United States	--	--	58.3	meta analysis of 64 studies
Anderson (1992)	United States	1990	250,000 - 350,000[3]	95	adjustment of 1976 NINDS [4] survey
NHIS[2] (1991)	United States	1985-89	182,891[3]	102.2 (75.4 - 129.1)	national survey (NHIS[2])
Wynn (1990)	Olmsted Co., Minnesota	1985	50[3]	159.8 (113 - 207)	ongoing surveillance
Helmick (1989)	Key West, Florida	1985	32[3]	70.1	cluster investigation
Baum (1981)	United States	1976	122,873[3]	57.8	NINDS[4] survey
Hoffman (1981)	Los Alamos Co., NM	1979	14[6]	75.7 (41.4 - 126.9)	cluster investigation

[1] adapted from Minden et al. (1993). Reference 1.

[2] National Health Interview Survey (NHIS) conducted annually by the National Center for Health Statistics

[3] possible, probable, and definite cases

[4] National Institute of Neurological Disorders and Stroke (NINDS)

[5] definite and probable cases

[6] definite cases

Table 5. - Sex-and age-specific prevalence estimates for Olmsted County and the combined study cohort.

AGE GROUP	MALES		FEMALES		TOTAL[1]	
	Olmsted County Prevalence Estimate per 100,000	Combined Cohort Prevalence Estimate per 100,000	Olmsted County Prevalence Estimate per 100,000	Combined Cohort Prevalence Estimate per 100,000	Olmsted County Prevalence Estimate per 100,000	Combined Cohort Prevalence Estimate per 100,000
0-34	29	N/A[2]	72	N/A[2]	51	N/A[2]
35-44	124	0	433	0	282	0
45-54	150	136	432	551	291	342
55-64	293	289	676	270	492	278
≥65	90	0	370	0	266	0

[1] missing age for five students.

[2] Not applicable. There are no cohort members in the 0-34 age group.

Table 6. - Sex-and age-specific prevalence estimates from the 1989-1994 NHIS surveys and the combined study cohort.

AGE GROUP	MALES		FEMALES		TOTAL [1]	
	NHIS Prevalence Estimate per 100,000	Combined Cohort Prevalence Estimate per 100,000	NHIS Prevalence Estimate per 100,000	Combined Cohort Prevalence Estimate per 100,000	NHIS Prevalence Estimate per 100,000	Combined Cohort Prevalence Estimate per 100,000
<30	8	N/A [2]	29	N/A [2]	18	N/A [2]
31-40	57	0	156	0	107	0
41-50	119	0	306	436	215	215
51-60	119	356	227	425	175	392
61-70	87	0	193	0	145	0
71+	37	N/A [2]	99	N/A [2]	74	N/A [2]

[1] missing age for five students.

[2] Not applicable. There are no cohort members in the< 30 and 71+ age groups.

Table 7. - Sex-and age-specific prevalence estimates for Olmsted County and the Mesita cohort.

AGE GROUP	MALES		FEMALES		TOTAL[1]	
	Olmsted Prevalence Estimate per 100,000	Mesita Prevalence Estimate per 100,000	Olmsted Prevalence Estimate per 100,000	Mesita Prevalence Estimate per 100,000	Olmsted Prevalence Estimate per 100,000	Mesita Prevalence Estimate per 100,000
0-34	29	N/A [2]	72	N/A [2]	51	N/A [2]
35-44	124	0	433	0	282	0
45-54	150	187	432	737	291	464
55-64	293	411	676	368	492	388
≥65	90	0	370	0	266	0

[1] missing age for five students.

[2] Not applicable. There are no cohort members in the 0-34 age group.

Table 8. - Sex-and age-specific prevalence estimates from the 1989-1994 NHIS surveys and the Mesita cohort.

AGE GROUP	MALES		FEMALES		TOTAL [1]	
	NHIS Prevalence Estimate per 100,000	Mesita Prevalence Estimate per 100,000	NHIS Prevalence Estimate per 100,000	Mesita Prevalence Estimate per 100,000	NHIS Prevalence Estimate per 100,000	Mesita Prevalence Estimate per 100,000
<30	8	N/A [2]	29	N/A [2]	18	N/A [2]
31-40	57	0	156	0	107	0
41-50	119	0	306	577	215	289
51-60	119	506	227	581	175	545
61-70	87	0	193	0	145	0
71+	37	N/A [2]	99	N/A [2]	74	N/A [2]

[1] missing age for five students.

[2] Not applicable. There are no cohort members in the< 30 and 71+ age groups.

Table 9. - Standardized morbidity ratios (SMRs) for the combined study cohort using selected U.S. Studies for comparison.

Reference Study	Expected Cases	Observed Cases	SMR	95% CI[1]
NINDS National Survey (Baum 1981)	6.8	14	2.05	1.12 - 3.43
Olmsted County (Wynn 1990)	18.0	14	0.77	0.42 - 1.30
NHIS National Survey (1989 -1994)	9.7	14	1.42	0.78 - 2.40

[1] Fisher's Exact

Table 10. - Standardized morbidity ratios (SMRs) for the Mesita study cohort using selected U.S. Studies for comparison.

Reference Study	Expected Cases	Observed Cases	SMR	95% CI[1]
NINDS National Survey (Baum 1981)	5.0	14	2.80	1.52 - 4.66
Olmsted County (Wynn 1990)	13.3	14	1.05	0.57 - 1.76
NHIS National Survey (1989 -1994)	7.2	14	1.93	1.06 - 3.24

[1] Fisher's Exact

APPENDIX A - SITE MAP

El Paso, Texas

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