ABSTRACT

The exact cause of Multiple Sclerosis (MS) in humans has not been determined. Animal models of demyelination suggest an immunological pathology, but this has never been proven for human cases of MS. A cluster of MS which occurred in a specific geographical area was investigated to possibly determine new risk factors for the cause of the disease. Genetics, phenotypes, elements of childhood—specifically location of home and school, nutrition, supplementation, viruses, animal exposure—both childhood and adult exposure to toxins, and adult occupation, were each studied for contributions to development of MS in adulthood. A survey was conducted to gather information about all identified factors from participants in the study. A control group was age- and sex-matched in number with the MS sample. No single factor which differed from the control group was dominant in the MS sample except location and proximity to xenobiotics. Childhood dietary patterns with greater consumption of cereals and red meat ($p < 0.05$) may have been protective in the control group; this was surprising to discover. No single food source appeared in causation of MS. Environmental exposures to heavy metals and chemicals could initiate MS during the developmental age and maintain the disease processes. Genetic polymorphisms of cytochrome P450 (CYP450) may be influential. Astrocytes, glial cells in the central nervous system (CNS), as an alternative to immune cells, are possibly the primary mechanism behind the pathogenesis of MS. This implies that the current paradigm of MS focused on autoimmunity is in need of review. Given that xenobiotics will continue to be a part of the environment, implementation of nutritional measures could possibly lessen xenobiotic burden through detoxification support.

INTRODUCTION

Multiple sclerosis (MS) is a complex disease of a heterogeneous nature. Its etiology has caused much controversy, and still remains unknown in the medical community after decades of research (1). The first description of MS as a neurological condition that afflicts the myelin sheath insulating long extensions of the axon conducting electrical signals from one neuron to another, was by "Carswell from Scotland and Cruveilhier from France in the 1830s" (2). The accepted classification of MS is as an "autoimmune" disease (3), yet it has not been proven that the human pathology is linked to an attack by the cellular immune system or a virus (2, 4-6). Animal models of demyelination have only been assumed as a valid extrapolation to the human disease (2, 6).

MS is identified as a disease of young adulthood and does exist worldwide. It is rare in some ethnic groups (e.g. Japanese), does not occur in other groups (e.g. African Blacks, Eskimos, Inuits, and Aborigines) (7) and appears to have high risk in other groups (e.g. Sardinians and Palestinians) (8). Distance further from the equator, latitude and cold climate are implicating factors in the occurrence of MS (9-11). Vieth (12) and others (10, 11) propose a connection to levels of vitamin D3 provided by natural sunlight. Milk and meat intake (13, 14), animal exposures (15-17), asthma (18), vaccines (19), allergy (20), free-radical damage (21), mercury-amalgam fillings (22), metalloproteinases (23) and vitamin B12 deficiency (24) have also been hypothesized as being causative. One previous cluster analysis found significance only in that the female MS patients abused drugs (1).

The purpose of this study was to seek the factor(s) which created vulnerability within the East Boston and Winthrop, MA cluster. In order to suggest what human MS is, and why it is acquired up until the time of puberty, then remains latent and becomes symptomatic in young adulthood, a chemical theory is reintroduced (22, 25, 26), but with disregard for the autoimmune argument.

It is proposed that local presence of toxic xenobiotics (see Table 1) played a primary role in creating vulnerability to MS.

Secondary factors of genetics, viral exposures, and nutrition, may have contributed to the vulnerability for the pathology of MS. Continued exposure to, or residual effects of, chemicals are hypothesized to be both the mitigating factor and the cause of the disease's progression.

Children are vulnerable to effects of xenobiotics during periods of growth and development (27, 28). Environmental toxins can potentially impact the immune system (29, 30), and perhaps overwhelm other immature and rapidly changing systems. It may even be plausible to consider whether development is completed optimally, as complete myelination of the brain does not appear to conclude until adulthood (31). White et al. (32) describe how cholesterol esters that are supposed to disappear with the maturation of myelin actually remain present in MS, suggesting a dysfunction both in the myelin and the myelin-generating glial cells or oligodendrocytes.

TABLE 1

Partial List of Xenobiotics Exposure in the Environment of East Boston and Winthrop, MA		
	Particulate matter	Gaseous Compounds
a. Diesel Trucks and Buses[1]	Elemental Carbon Sulfate Nitrate Metals Trace Elements Water Ultra fine particles (<100 nm)	Carbon monoxide Carbon dioxide Nitrogen compounds (NOx) Sulfur compound (SO2) Low-molecular weight hydrocarbons and derivatives (i.e. aromatic hydrocarbons) Toluene Benzene
b. Flight Tracks and Runway Emissions[2]	Lead Copper [Cu(I) & Cu (II)] Trace Metals (i.e. Zn, Cu, Pb, Cd, Fe, and Ni) Particulate Matter 10 (PM10) Volatile Organic Compounds (VOC), precursor to Ozone (CO3)	Carbon Monoxide NOx SO2 Aromatic hydrocarbons (i.e. toluene, xylene and benzene) Polycyclic aromatic hydrocarbons (i.e. benzo(a)pyrene and chrysene)
c. Gasoline combustion from automobiles (highways and Callahan/Sumner Tunnel Vents)[3]	Particulate matter10	CO NOx & NO2 SO2 Organic compounds (i.e. Formaldehyde) Acids (Acetic) Aldehydes Organic Hydrocarbons
d. Coal-Burning Factory[4]	Mercury	Sulfur Oxides (SO2) Nitrogen Oxides (NO2) Acids Organic hydrocarbons
e. Funeral Home		Formaldehyde

[1] Source- U.S. Environmental Protection Agency (EPA). (2002) Health assessment document for diesel engine exhaust. Prepared by the National Center for Environmental Assessment, Washington, DC, for the Office of Transportation and Air Quality; EPA/600/8- 90/057F. 2002.

[2] Source- Brabander, Dan Prof., Forina, Anna, Phillips, Paige, Vigliotti, Lauren. Contamination of Belle Isle Marsh as Determined by Trace Metal Analysis. 1999. Dumser, JB. Review of Logan Soot Studies. 1999. Logan Airside Improvements Planning Project. Appendix F, Air Quality. Supplemental DEIS/FEIR 1998. Logan Airside Improvements Planning Project. Environmental Consequences*:* Air Quality/Odors.

BACKGROUND

The author was enrolled in the 1994 investigation by Charles Poser, MD, Senior Neurologist at the Beth Israel Hospital and lead author of the Poser Criteria for clinical diagnosis of MS (33), into the possible cause of the cluster of Multiple Sclerosis in East Boston, and Winthrop, MA. Poser had previously noted clusters reported in two other communities in Massachusetts, as well as in other states (7).

Poser's survey of 1994 was conducted by telephone interviews and subjects were asked details concerning childhood schools, playgrounds, viruses, waste dumps, trauma, etc. No doubt the childhood history was imperative, since experts of the disease have noted that there is "the existence of a critical age before puberty, between 13-20 years of age, for exposure to the putative environmental agent"(34), MS "is acquired between 5 and 15years" (35) and "susceptibility extends from age 11 to 45…ordinarily acquired in early adolescence with a lengthy latency before symptoms onset"(36). Emigration patterns of MS indicate the implication of puberty as persons emigrating from areas of high risk to low risk before 15 years acquire the low risk of the destination (7, 37), and vice versa.

The 1994 investigation of the East Boston and Winthrop, MA cluster resulted in no conclusion about the cause of MS in this area.

The identification of clusters of MS has also occurred in the following U.S. locales: Wellington, OH (1998-2000); Galion OH,(1986)(38); De Pue, IL (1971-1990);

Supplemental DEIS/FEIR. McBride, David. Chemicals in Jet Fuel Emissions. Washington State Department of Health, Office of Environmental Health Assessment Services, 1999

[3] Source- American Industrial Hygiene Association, Air Pollution Manual, Part (Evaluation), 2nd Ed. Westmont, NJ; AIAH, 1972; Schattenek, G and Wan, P. Air Quality Assessment Techniques for Roadway Tunnel Projects, 1996. 96-RP108B.05. *www.airmetrics.com/products/studies/96-RP108B.htm*

[4] Source-American Industrial Hygiene Association, Air Pollution Manual, Part (Evaluation), 2nd Ed. Wstmont, NJ; AIAH, 1972.

Mansfield, MA (1971)(39); Key West, FL (1985)(39-41); Rochester NY (1987); Henribourg, Saskatchewan (42); Mossyrock, WA(40, 43); El Paso, TX (at www.atsdr.cdc.gov/elpaso/pubcom.html). These previous cluster investigations did not implicate autoimmunity as the cause of MS, but rather heavy metals (e.g. mercury), minerals, waste disposal areas, soil and water contamination, smelters, foundries and industry. Additional clusters may be forthcoming as the federal Agency for Toxic Substances and Disease Registries (ATSDR) has recently awarded grants to five investigators who are studying the possible environmental risk factors in MS and ALS clusters within the states of Illinois, Texas, Massachusetts, Oregon and Missouri.

In other areas of the world, clusters have been identified in Canada(44), Denmark (45), Poland (46), the Orkney Islands (47), and Finland (48).

Hogancamp et al. say, "Reports of clusters, small epidemics, geographic variation in prevalence, and alteration of MS susceptibility by migration support an environmental factor (or factors)" (49). It may be important that "immigration to a new country can represent a substantial change in a person's diet, life style, and environment, and these changes may each alter the metabolism of xenobiotics and endogenous hormones that play a role in carcinogenic response"(50). MS is not regarded as a carcinogenic response, yet chemotherapeutic agents (e.g. cytoxan and methotrexate) are said to be beneficial as a form of MS treatment, and the relevance of immigration within both disease processes has been noted (51-53).

The survey used in this thesis (Appendix 1) was created with both the current paradigm of the disease and the hypotheses of this thesis in mind. Its basis was a 5 year extensive review of the literature on possible etiology and epidemiology of MS, including

profession (54). Excess mortality among young teachers from autoimmune diseases, such as MS, is thought to arise from some type of occupational exposure (55). Consideration was given to the already specific postulates about the roles of genetics (56), viruses (15-17, 57-59) and trauma (33, 60). For the purpose of this thesis, determinations were made in nutritional intake up to age 18 years, along with environmental exposures and occupational exposure to xenobiotics. Proximity to sources of pollution, toxins and hazards, and length of exposure were important to support the hypothesis and investigate any possible impact on disease risk.

Dietary and nutritional influence on MS have yet to be given serious consideration (61) or rigorous testing by the field of neurology, and still remains in controversy (62, 63). Similar to Kurtzke et al.(64), childhood dietary patterns of specific food groups were assessed in both MS and non-MS samples, however the specified foodstuffs of the former study by Kurtzke et al. has not been ascertained.

Details about multivitamin and cod liver oil supplementation were not included in the Kurtzke study, but were in this study. The importance of vitamin supplementation in relation to chronic disease was recently suggested by Fletcher et al. Their suggestion was that because "most people do not consume an optimal amount of all vitamins by diet alone" there may be an increased risk for several chronic illnesses (65).

The addition of cod liver oil supplementation was included in the MS protocol of Dr. Roy Swank. As a clinical neurologist, Swank proposed to his MS patients a low saturated fat diet, supplemented with multivitamins and cod liver oil. Those who adhered to his diet and supplementation, were observed to be "ambulant and normal in all respects" (62, 66) after fifty years.

MATERIALS AND METHODS

The survey used (Appendix 1) was formulated by the author. It consisted of eighteen questions, and was analyzed by SPSS software for Windows. Approximate time to complete the telephone survey was fifteen minutes per subject.

Total number of subjects was forty-eight (N=48). The subjects surveyed for the MS sample were twenty-four MS patients, who were formerly born and/or raised in East Boston or Winthrop, or presently live in either location. The subjects surveyed for the control group were twenty-four non-MS patients, who were born and raised in a variety of geographical locations. The control group was age- and sex-matched to those with MS. Eight males and sixteen females volunteered to participate in the MS sample, thus the ratio of females to males was 2:1.

The procedures to acquire participants began in September 2002 and continued for seven months. Flyers were placed in strategic public locations within the communities of East Boston and Winthrop, as well as surrounding communities, where residents originally from East Boston and Winthrop may have moved. One notice and two articles were written in newspapers to attract interest; notification ran on community cable television and some subjects learned of the study via word-of-mouth.

Most of the participants of the current study were not the same as participants of the 1994 study and therefore additional MS cases to those of the Poser study.

All surveying and acquisition of data was conducted by telephone. The author made several observational automobile trips to the local areas; streets on which MS subjects lived and attended schools, both in East Boston and Winthrop (see Appendix 2).

This provided a first-hand, present day view of what environmental exposures exist, as well as what previous exposures needed to be researched for correlation to the childhood years of the MS sample. Authorities in the domains of politics, community advocacy, and environmental health (e.g. Massachusetts Department of Environmental Protection), were all contacted by telephone to provide historical facts and to acquire verification of transportation, manufacturing, and commerce information. Historical information relating to immigration patterns, and industry for the area of East Boston were obtained at the Meridian Street and Main branches of the Boston Public Library.

Limitations were 1) the inability to survey all from East Boston and Winthrop who have developed MS 2) recall bias of the subjects 3) retrospective observation by the subjects 4) sample size and 5) the inability to survey the heterogeneous locations of the homes and schools of the non-MS sample.

RESULTS

1. Current Age

The mean (SD) of the current age of the entire sample (N=48) was 50.7083 ± 1.5417 years, ranging from 30-80 years. Current age range for the MS sample (N=24) was 30-80 years and for the non-MS sample was 30-72 years.

2. Age of Multiple Sclerosis Diagnosis

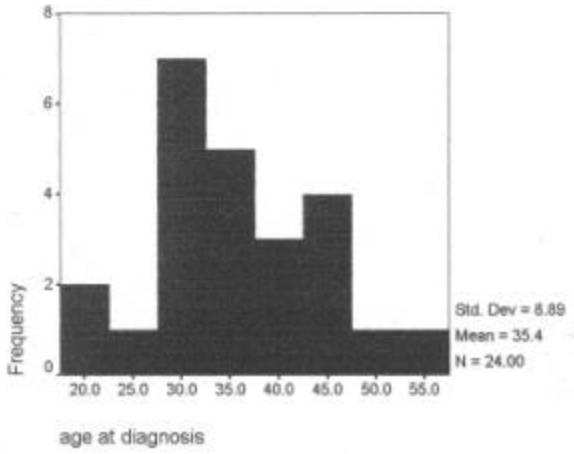


Fig. 1: Age of Diagnosis in MS sample

The mean (SD) age of diagnosis with MS was 35.3750 ± 1.1846 years. Age for diagnosis in the MS sample (N=24) ranged from 20-54 years (Fig. 1).

3. Location and time periods of homes

The homes and streets on which the MS sample lived resulted in the following proximity to sources of pollution: 72.5 % of the MS sample lived in areas of Mobile Sources of pollution; 17.8% lived close to Major Sources and 9.7% lived with Area Sources (TABLE 1). The time span of living in these areas ranged from 5-44 years.

TABLE 1

Sources of Pollution	Mobile	Major	Area
Homes in close proximity	72.5%	17.8%	9.7%

(Table from US EPA America's Children and the Environment: Measures of Contaminants, Body Burdens and Illnesses pg.29, 2003. There are three general categories of pollution sources:
1) Mobiles Sources- on-road sources such as cars, light trucks, large trucks, and buses, and non-road sources, such as farms, construction equipment, lawn and garden equipment, marine engines, aircraft or locomotives. For the purpose of this study, these are identified as major highways and related, fly over patterns of aircraft, diesel trucks, fuel trucks and diesel buses
2**) Major Sources**-large industrial facilities such as chemical manufacturing plants, refineries, and waste incinerators. These release air toxics by leaks, transfer of materials, or discharge via stacks or vents. For the purpose of this study these are identified as petroleum farms, Callahan/Sumner tunnel ventilation buildings and runway emissions
3) **Area Sources**- small stationary facilities such as dry cleaners. For the purpose of this study these are identified as a coal-fired gumball factory and funeral home.)

4. Location and time periods of schools

The schools attended by the MS sample resulted in the following proximity to sources of pollution: a) Grammar school-56.3% near Mobile, 30.4% near Major and 13.3% near Area Sources. Most children (77.9%) attended these schools 5-8 years; b) Middle/Junior high school – 61.2% near Mobile Sources and 38.8% near Major Sources. The children attended 2-4 years; c) High school- 60% near Mobile Sources and 40% near Major Sources. The majority (90.9%) attended for 4 years (TABLE 2).

TABLE 2

School Years	Number of Years	Mobile	Major	Area
Grammar School	5-8 years	56.3%	30.4%	13.3%
Middle or Junior High	2-4 years	61.2%	38.8%	
High School	4 years	60%	40%	

(From US EPA America's Children and the Environment: Measures of Contaminants, Body Burdens and Illnesses pg.29, 2003.)

5. Ethnicity, phenotype and familiar medical diagnoses

Ethnicity in the non-MS sample (N=24) resulted as 29.2% Italians; 50% Irish or a mix (mix is 50% Irish and 50% of another ethnicity); 12.5% Ashkenazi Jew; 4.2% Greek and 4.2% Portuguese. Ethnicity of the MS sample (N=24) resulted as 75% Italians or mix; 16.7% Irish or mix; 8.3% as Ashkenazi Jew (TABLE 3).

TABLE 3

Ethnicity for MS sample	Italian or Italian mix	Irish or Irish mix	Ashkenazi Jew
	75%	16.7%	8.3%

Light hair, within three degrees of relation, was present in 70.8% of the non-MS sample, and was present in 62.5% of the MS sample.

Blue eyes, within three degrees of relations, were present in 79.2% of the non-MS sample, and was present in 54.2% of the MS sample.

The specified health conditions of the survey were not remarkable in all study subjects.

The specified health conditions of the survey for relations within three degrees were not remarkable in all study subjects except for Type II, Non-Insulin Dependent Diabetes Mellitus (NIDDM). This adult-onset condition was positively recalled for relatives by 62.5% of subjects within the MS sample and by 62.5% in the non-MS sample.

6. Familial occurrence

Familial occurrence of multiple sclerosis within the MS sample was 30.4%, or seven of the twenty-four subjects. The relatives had all shared in the environment of East Boston.

7. Childhood dietary patterns

Nutrition assessment of dietary intake for the entire sample, up to age eighteen, was as follows (TABLE 4):

TABLE 4

Sample	Pasta[o] [2]	Bread[2]	Cereal[2]	Fish[1] [2]	Red Meat[2]	Milk[2]	Eggs[2]	Fruits & Vegetables[3]
MS	Low 86.4%	High 95.5%	Mod 50.0%	Low 87.5%	Low 68.2%	High 62.5%	Low 54.5%	Low 81.8%
Non-MS	Low 70.8%	High 87.5%	**High** 66.67%	Low 90.9%	**Mod** 54.2%	High 87.5%	Low 66.7%	Low 70.8%

[o]The representation of Pasta here is as the main course of a meal.
[1] An Average of 62.5% of the fish was identified as white fish, i.e. haddock, flounder, cod or pollock, and therefore, not a source of omega-3 PUFA, EPA or DHA.
[2]Low- food intake limited to 2 or < times in a 7 day period; Moderate- food intake 3-4 times in a 7 day period; High- food intake 5+ times in a 7 day period
[3] Low- 10 servings or <; Moderate 11-25 svgs. and High- 25+ svgs. in a 7 day period, based on the "5 a day" principle for fruit and vegetable intake (67, 68).

8. Multivitamin/mineral and cod liver oil supplementation

Multivitamin supplementation during childhood did not occur in 66.7% of the non-MS sample and did not occur in 70.8% of the MS sample.

Cod liver oil supplementation during childhood did not occur in 70.8% of the non-MS sample, and did not occur in 91.7% of the MS sample.

9. Occupations

Occupations from the age of sixteen years to present, within the non-MS and MS samples resulted in the following (TABLE 4):

TABLE 4

Occupational Group	*MS sample*	*Non-MS sample*
Business/ secretarial	33.8%	**20.2%**
Airport Related	14.68%	**13.13%**
Food Service	10.1%	**7.5%**
Healthcare	6.63%	**14.38%**
Construction/trade/manufacturing	8.05%	**7.9%**
Academics/child care	4.95%	**14.8%**
Retail	12.98%	**11.05%**
Professional	3.85%	**6.05%**
Hairdressers/dry cleaners	1.4%	**3.33%**
Military	**3.58%**	**0**

10. Viral and bacterial infection and canine distemper virus exposure

Viral or bacterial illnesses, specific to those designated in this survey, presented clinically in the entire sample as follows (TABLE 5):

TABLE 5

	Mumps	Measles	Mononucleosis	Pneumonia
MS	54.2%	58.3%	25%	12.5%
Non-MS	41.7%	66.7%	12.5%	12.5%

Exposure to Canine Distemper Virus (CDV) occurred in 4.2% of the non-MS sample and 12.5% in the MS sample.

11. Allergy shots

Allergy shots, which are a form of immunotherapy to desensitize a person to allergens, were administered to 16.7% of the non-MS sample, and 20.8 % of the MS sample.

12. Trauma and surgery

Trauma or major surgery prior to the age of twenty years was experienced by 25% of the non-MS sample, and 41.7% of the MS sample.

DISCUSSION

The mean age at time of diagnosis, 35.3750 ± 1.1815 years, was consistent with previous investigation that the majority of MS cases are diagnosed between 20-40 years of age (69).

The resulting gender ratio of those that volunteered to participate, two females for every one male, also agreed with previous reports that MS occurs more often in females than in males (70).

The significance of higher Italian heritage (58.3% Italian, 16.7% Italian mix) vs. an Irish heritage (4.2% Irish, 12.5% Irish mix) in the MS sample bordered on being statistically significant ($p < 0.05$). This may be due to chance or a result of an Italian immigration to East Boston from 1855-1915, following the first immigration to East Boston by the Irish, who immigrated as a result of the Potato Famine in Ireland during the 1800s. This also may be relevant to the argument that Poser proposed that the voyages of the Vikings spread a "genetic susceptibility" to geographical locations such as southern Italy and the island of Sicily (71). The non-MS group was 29.2% Italian vs. 12.5% Irish and 37.5% Irish mix.

Interestingly, more than 50% of each study group had the features of light hair/blue eyes in the family within two degrees of relation. This would have been expected given the Irish predominance in the non-MS group, but maybe relevant since the MS sample was mostly Italian. The familiar Nordic appearance is of the red/blonde hair and blue eyes, and 90% of the Vikings had light eyes. There appears to be need for further investigation, given the locations of MS within the country of Italy(72-76).

This MS sample was also only represented by Ashkenazi Jews. Poser made note of selectivity among this Jewish lineage for MS in the country of Israel (7).

Within dietary patterns through the age of eighteen, there was a statistical significance in the consumption of cereals and red meat between the MS sample and the control. The control group consumed more cereal and red meat than did the MS group. The cereal component may be the fortification with vital B vitamins and folic acid (folate); the red meat could represent the impact of protein content on the metabolism of chemicals (77). Vegetarian, or under-nourished humans, have been shown to reverse the enhanced metabolism of xenobiotics brought about by a protein-rich diet (50). Red meat is also a rich source of iron and a higher level of iron may decrease the toxicity and/or burden of heavy metals. Iron may also modify the Phase 1 mixed function oxidase system, by which the liver metabolizes xenobiotics (77) .

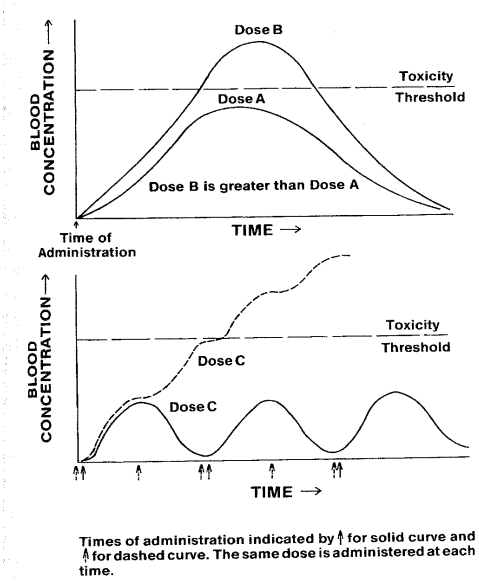
Cereal may have been an insurance of levels of the B vitamins, as fortification of breakfast cereal with B vitamins began at the time of World War II. Riboflavin (vitamin B2) deficient animals have been shown to have reductions in the ability to metabolize a number of xenobiotics, including benzo(a)pyrene (78).

The familial occurrence of MS was greater at 30.4% than anticipated based on previous research in which " the prevalence of familial MS in first-degree relatives is 5-10%" (79). This is perhaps indicative of the strong influence of environment in East Boston and Winthrop, MA. Since it appears no relatives of the MS sample that lived outside of studied geographical area developed MS, then environment is the causal factor and not genetics.

What some previous theories would have predicted did not occur in the outcome of this research. The remaining factors (e.g. Northern European descent, asthma, Type 1 diabetes, food allergies, cod liver oil supplementation, occupation, measles and mononucleosis infection, canine distemper exposure, trauma or surgery) indicated no statistically significant difference ($p < 0.05$) between the MS sample and the control. This was not expected given preceding theories of causation. If, like Kurtzke et al. found in the Faroe Islands study (64), occupation, dietary history, animal exposure, illnesses, operations and injuries did not differentiate the MS group in the East Boston and Winthrop geographical area from the control group, it appears that the possibility of low level, chronic xenobiotics, including heavy metals in the local environment, may be the differentiating factor.

The inferred predisposing risk factor for the MS sample was location in East Boston and Winthrop, MA. The xenobiotic byproducts of the commercial and industrialized area (TABLE 1) are known to impact the homeostasis of the body and brain. Kamrin has noted that multiple xenobiotics exposures "may produce no more effect than a single exposure ((80)…if the dose is too low to cause any adverse effects and is excreted by the body before another dose is administered." If, however, the time between exposures is very short and does not allow for complete excretion, the increasing chemical concentration in the blood reaches a toxic level, even if each single dose is not strong enough to be toxic (Fig. 2). The body's response depends on the "formation of toxicant-receptor complexes," such that higher doses lead to a higher concentration of these complexes, which create a stronger toxic effect. Years of repeated low-level exposure to xenobiotics may thus result in recurrent or chronic reactions.

Fig. 2: Relationship between exposure time and blood concentration of toxins



(From Kamrin, MA. Toxicology: A Primer on Toxicology Principles and Applications. Pg. 31, 1988.)

The toxic effects can take years to develop and present themselves, as does the disease of MS, which takes years to develop and present clinically with relapsing-remitting or chronic symptoms; both display a period of latency.

Systems do exist within the organs whose mechanism is to metabolize and prevent possible tissue toxicity of xenobiotics and heavy metals. The adaptation to metabolize and detoxify foreign chemicals involves one enzyme system known as the Cytochrome P450s. Sometimes, during the metabolism of the original substrate, more toxic or mutagenic metabolites are produced, so even an altered expression of detoxification enzymes, determined by genetic polymorphisms (81), can have profound toxicological consequences. The metallothioneins and the choroid plexus within the brain help with heavy metal ions and their neurotoxic potential.

Cytochrome P450

The responsibility for clearing and removing undesirable and toxic environmental chemicals (82, 83) is the role of the Cytochrome P450s (CYP450), a “superfamily of

heme-thiolate proteins." These enzymes are diverse in the reactions they catalyze and can act on an extensive range of chemically dissimilar substrates. CYP450s "support the oxidative, peroxidative and reductive metabolism of such endogenous and xenobiotic substrates as environmental pollutants, agrochemicals, plant allelochemicals, steroids, prostaglandins and fatty acids (84)." Some of the exogenous substrates include disruptors of both endocrine (85) (Our Stolen Future) (e.g. lead, cadmium and PCBs), and cellular homeostasis (86). The variants in CYP450 are known as isomers and these have a central role in Phase 1 xenobiotics metabolism. CYP450s can lead to heterogeneous pharmacological problems because these enzymes determine variability in drug and xenobiotics metabolism between individuals (84). It is the either the genotype, or the enzyme expression status, which determines how much of a xenobiotic will be necessary to show effect in an individual (87). The frequency of "allelic variants" exist among different populations (i.e. African-Americans and Caucasians)(88). Phenotypic variations between Caucasians, Blacks and Asians in a Phase 2 enzyme responsible for the detoxification pathway of acetylation is believed to determine the risk of bladder cancer (89).

CYP450 occur in a variety of tissues with diverse roles (83), (84). A CYP450 enzyme (P450arom) in the brain and liver appears responsible for reproduction and fertility (82) and another for production of female hormones (90). Two CYP450 isomers in leukocytes appear to change metabolism during pregnancy (91). Another isomer is responsible for the metabolism of the glucocorticoid dexamethasone (92). One form of allergic reaction within skin cells is thought to be determined by CYP450 (93). A new

CYP450 has been found that is primarily expressed in the brain and appears to have a mechanism in steroid metabolism, which is a possible element of cognitive function (94).

Subfamilies of most CYP have been identified in the brains of rats, and although scientific knowledge of the human brain CYP lags behind that of the liver, it is accepted that altered brain metabolism of xenobiotics, including toxins, could affect brain function, as well as development of diseases in humans (95). The minute levels of CYP isomers in the brain, compared to those in the liver, seem to have specific functions, e.g. regulation of GABA agonists, cholesterol homeostasis, and xenobiotic-induced neurotoxicity (96). Importantly, CYP450 content in the brain is "very responsive to environmental factors" (97), and the quantity of CYP450 is altered by the environment, i.e. drugs and chemicals.

Astrocytes

Within the CNS, the CYP450 isoform 2E1 is induced in astrocytes to metabolize the arachidonic acid of inflammation (98). Inflammation may be caused by lipopolysaccharides (LPS), acute phase cytokines such as IL-1beta, nitric oxide (NO) and reactive oxygen species (ROS). This CYP450 isoform 2E1 is also induced in astrocytes following mechanical injury to the brain (99). In the CNS, the 2E1 is responsible for metabolizing exogenous substrates such as anesthetics, organic solvents and ethanol (100).[5] In addition astrocytes are:

- The source of cytokines and alterations of CYP1A activity due to inflammation in the CNS (animals) and responsive to dexamethasone (102).

[5] Notably, it has been theorized that the "adverse hepatic events associated with Type II diabetes may be in part a result of enhanced CYP2E1 expression and activity"Wang Z, Hall S, Maya J, Li L, Asghar A ,Gorski J:
Diabetes mellitus increases the in vivo activity of cytochrome P450 2E1 in humans. Br J Clin Pharamcol 55: 77-85, 2003..

- The cells of the CNS more sensitive to Carbon Monoxide (CO) than neurons, and whose cellular respiration can be inhibited by CO with physiological presence of adequate oxygen (103); swelling and necrosis can occur as a result of acute CO exposure (104).

Tiffany-Castiglioni and Qian have stated, "The brain is an organ that concentrates metals" (105) and metals frequently deposit in astrocytes.

- The glial cells responsible for the buffering of essential metals, i.e. lead, mercury, manganese and copper. In high amounts metals become neurotoxic and depend on the astrocytes to protect against cytotoxicity (105).
- The CNS cells where lead (Pb) accumulates and binds to the endoplasmic reticulum (ER) (106, 107) with retention occurring by the sulfhydryl groups (107). Immature brain cells were shown to be more sensitive to lead in vitro, with astrocytes more sensitive than neurons. Those astrocytes that were not lost demonstrated astrogliosis and may play a role in the toxicity of lead seen during developmental years (108).
- The CNS cortical cells that are involved in the neurotoxicity of free Zn(2+) (109).
- The binders (110) and accumulators of manganese metalloproteins in the brain (111). Manganese is considered a possible aid to neural activity when it is released at the synaptic cleft, but also an essential trace metal toxicant because of its prooxidant activity.
- The CNS cells that preferentially accumulate methylmercury (MeHg), which can inhibit the uptake of glutamate, with "neuronal dysfunction being secondary to the disturbance in astrocytes" and causes the swelling of astrocytes (112, 113).

- The source of brain methallothioneins (MTs) which protect against the acute cytotoxic effects of MeHg, as well as resist the toxicity of other heavy metals (114). MTs have high levels of cysteine and a strong affinity for heavy metals (27). Primary astrocyte cultures express these sulfhydryl (-SH) containing proteins (115). The protection by astrocytes against MeHg is influenced by the levels of MT proteins available. Pretreatment with zinc helps MT be expressed at high levels, as well as make astrocytes resistant to swelling (116). A decrease in intracellular cysteine and cystine uptake in astrocytes (117, 118), and excessive generation of ROS by MeHg is seen as a possible way it produces neurotoxicity (119). The generation of "oxidative stress and excess N-methyl-D-aspartate (NMDA) receptor activation" may lead to neuronal demise (120). Interestingly, Zn-MT II treatment reduced severity of symptoms in an EAE experiment (121).
- The glial cells also modulating glutamate uptake (122) and offering protection by their high affinity to glutamate transport (123). Heavy metals and organic solvents may interfere with this neuroprotection. MeHg has been shown to decrease lactate formation from glutamate in the mitochondria of cultured astrocytes and lactate is an important substrate for neurons (124).
- The glial cells which not only provide cysteine to neurons, but prevent cysteine toxicity (catalyzed by oxidation by copper), by releasing pyruvate (125).

The roles of astrocytes are even more extensive and implicate them in manners beyond the primary antigen presenting cell (APC) in MS as already proposed by De Keyser et al. (126, 127). The possibility exists that the pathogenesis of MS is brought about by these glial cells that occupy 25% of the CNS volume (128), both because of the

above properties and because of other regulatory, supportive, trophic, antioxidant, homeostatic, and gliotic properties they exhibit in the brain and CNS.[6]

Choroid Plexus

Normal human cognitive processes can only occur under chemical stability in the brain. Humans can experience cognitive deficits when exposed to "environmental poisons (142)." That is one necessity for optimal integrity of both the blood-brain and blood-CSF barriers. Evidence indicates that the CNS possibly protects itself against toxic heavy metal ions via the cerebrospinal fluid (CSF) and the choroid plexus, the principal site of formation of the CSF (143, 144). When animals were administered lead, cadmium, mercury and arsenic into the peritoneum of the brain, it accumulated in the

[6] For further information, see Schroeter ML, Muller S, Lindenau J, Wiesner B, Hanisch UK, Wolf G ,Blasig IE: Astrocytes induce manganese superoxide dismutase in brain capillary endothelial cells. Neuroreport 12: 2513-7, 2001. and Schroeter ML, Mertsch K, Giese H, Muller S, Sporbert A, Hickel B ,Blasig IE: Astrocytes enhance radical defence in capillary endothelial cells constituting the blood-brain barrier. FEBS Lett 449: 241-4, 1999.; Mi H, Haeberle H ,Barres B: Induction of astrocyte differentiation by endothelial cells. J Neurosci 21: 1538-47, 2001.; Aschner M ,Allen JW: Astrocytes in methylmercury, ammonia, methionine sulfoximine and alcohol-induced neurotoxicity. Neurotoxicology 21: 573-9, 2000.; Miller RH, Fulton BP ,Raff MC: A Novel Type of Glial Cell Associated with Nodes of Ranvier in Rat Optic Nerve. Eur J Neurosci 1: 172-180, 1989.; Gard AL, Burrell MR, Pfeiffer SE, Rudge JS ,Williams WC, 2nd: Astroglial control of oligodendrocyte survival mediated by PDGF and leukemia inhibitory factor-like protein. Development 121: 2187-97, 1995.; Naveilhan P, Neveu I, Jehan F, Baudet C, Wion D ,Brachet P: Reactive oxygen species influence nerve growth factor synthesis in primary rat astrocytes. J Neurochem 62: 2178-86, 1994.; Neveu I, Naveilhan P, Jehan F, Baudet C, Wion D, De Luca HF ,Brachet P: 1,25-dihydroxyvitamin D3 regulates the synthesis of nerve growth factor in primary cultures of glial cells. Brain Res Mol Brain Res 24: 70-6, 1994.; Magistretti PJ ,Pellerin L: Cellular mechanisms of brain energy metabolism. Relevance to functional brain imaging and to neurodegenerative disorders. Ann N Y Acad Sci 777: 380-7, 1996.; Garcion E, Sindj L, Nataf S, Brachet P, Darcy F ,Montero-Menei C: Treatment of Experimental autoimmune encephalomyelitis in rat by 1, 25-dihydroxyvitamin D3 leads to early effects within the central nervous system. Acta Neuropathol (Berl) 105: 438-48, 2003.; Badaut J, Lasbennes F, Magistretti PJ ,Regli L: Aquaporins in brain: distribution, physiology, and pathophysiology. J Cereb Blood Flow Metab 22: 367-78, 2002.; Kurachi Y ,Hibino H: [Molecular dynamics of K+ transport and its crucial involvement in signal transduction]. Nihon Shinkei Seishin Yakurigaku Zasshi 23: 135-8, 2003.; Behan P, Chaudhuri A ,Roep B: The Pathogenesis of Multiple Sclerosis Revisited. J R Coll Physicians Edinb 32: 244-265, 2002.; Morcos Y, Lee S ,Levin M: A role for hypertrophic astrocytes and astrocyte precursors in a case of rapidly progressive multiple sclerosis. Mult Scler 9: 332-41, 2003.; Brunello A, Weissenberger J, Kappeler A, Vallan C, Peters M, Rose-John S ,Weis J: Astrocytic alterations in interleukin-6/Soluble interleukin-6 receptor alpha double-transgenic mice. Am J Pathol 157: 1485-93, 2000.; Mutinelli F, Vandevelde M, Griot C ,Richard A: Astrocytic infection in canine distemper virus-induced demyelination. Acta Neuropathol (Berl) 77: 333-5, 1989.; Watkins LR, Milligan ED ,Maier SF: Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. Adv Exp Med Biol 521: 1-21, 2003.; He J, McCarthy, M, Zhou Y, Chandran B, Wood C: Infection of primary human fetal astrocytes by human herpesvirus 6. J Virol 70(2):1296-300, 1996.

lateral choroids plexus. Cystine occurred in high levels in the choroids plexus, and it appears that it protects the CSF and brain from fluxes of toxic heavy metals in the blood, that could result in neurotoxicity.

Examples of Exogenous factors that impact Cytochrome P450

- Copper II ions have been shown to inhibit CYP450 (145).
- Surgical stress puts the CYP3A4 enzyme activity into decline and that also affects other substrates of this enzyme, such as drugs (146); one-half of drugs prescribed today are substrates for CYP3A4 (147).
- Psychologically stressful events can elevate cortisol, and have been shown to significantly increase TNF-alpha the day after the event (148). As a cytokine, TNF-alpha is known to regulate the CYP450 (149).
- Any interferon producing process, i.e. inflammation, infection, infectious disease or vaccines may depress the expression and activity of CYP450 enzymes and/or induce others (150-153). Interferon production mediates the loss of mRNA of these enzymes (150, 152). Less synthesis of enzymes occurs in the liver and this can alter the manner of drug clearance and toxic activation (154, 155). Interferon alpha/beta were shown to produce such a depression on the induced CYP450 isomers, again lessening the bioactivation and detoxification of xenobiotics (156).
- In addition to the cytokines IFN and IL-1, TNF-alpha and IL-6 can also regulate the CYP450 (149).
- The levels of vitamin C (ascorbic acid) can affect the liver microsomal CYP450, such that in animals a deficiency of ascorbic acid results in a decrease in drug metabolism (157). When enzymes of CYP450 or peroxidases are metabolizing xenobiotics, free

radicals are formed and antioxidants, such as vitamin C can help protect against the toxicity of the oxidation (158). In tissues that bind cadmium, ascorbic acid levels may be reduced (159).

- The inclusion of fish oil into the diet, over other oil forms, has been shown to impact the liver enzyme and antioxidant systems in a beneficial manner (160, 161). Fish oil has been suggested to benefit MS (162, 163).
- Polyunsaturated fatty acids (PUFA) and essential fatty acids (EFA) were shown to optimize microsomal enzyme activity over diets that were fat-free in animals (77).

Examples of exogenous factors that affect metallothioneins

Zinc can impact upon the metallothionein system in a way that allows the resistance to toxic Methylmercury (MeHg) (85, 116). Too much zinc, however, can disrupt the metabolism of iron (77).

Examples of exogenous factors that affect heavy metal concentrations

- Sulfur-containing amino acids, i.e. methionine, cysteine, cystine, glutathione and histidine help in detoxification of heavy metals. Sulfhydryl groups (-SH) have the ability to bind (115) heavy metals in tissue and enzymes. A deficiency of these specific amino acids may not clear heavy metals (164), due to the conjugation (Phase 2) property of sulfur. Providing sulfur-containing foods may help clear toxins, and may be why high consumption of eggs were found to decrease the risk for breast cancer (165). Lucas et al. recently found that interferon beta-1a, a current therapy for MS, raised the serum level of reduced –SH groups in MS patients, which were found to be lower than in controls (166).

- It has been concluded that reduced seasonal sunlight levels (source of vitamin D3) cause elevated blood concentration of lead during the winter (167). Serum 25OHD and 1,25(OH)2D3, the bioactive metabolites of vitamin D, are lower during the winter months (Dec-Mar) (168). Sunlight is inversely proportional to mortality from MS (169) and exposure to winter sun appears to have influenced risk of MS (170). If an animal study can be extrapolated to humans, sex, age and season also determined the concentrations of cadmium and mercury (171).
- Cadmium, copper, lead and zinc concentrations in air "were found to be higher in the cold and more stable air conditions" of the winter season (172). Wind direction from industrial areas and elevation were other determinants of metal concentrations in the air. (Wind and elevation also are determinants in deposits of synthetic chemicals worldwide.)
- Pregnancy has been shown to alter the lead (Pb) levels in mothers (173) with the postpartum period displaying the highest lead concentrations and perhaps being resolved by proper calcium supplementation (174).
- Vitamin E deficiency in animals appeared to enhance the toxicity of lead exposure (78).

Lipid storage of and mobilization of xenobiotics and myelin

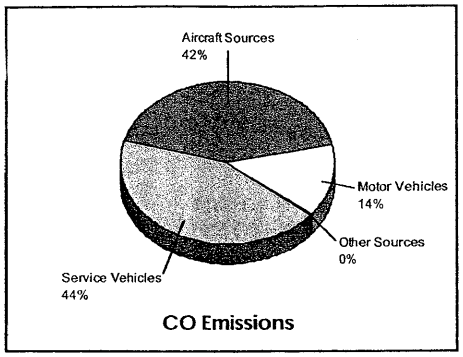
The brain and myelin are tissues of a predominant lipid composition (175). Many xenobiotics are lipophilic, with the capacity to cross cell membranes, such as the BBB, and take up storage in adipose or fatty tissue (176). It is believed that the intracellular

storage of lipophilic xenobiotics may depend on the carrier role of lipoproteins (e.g. VLDL, LDL and HDL) (177). The fat stored xenobiotic compounds have the capacity to be mobilized and released back into the bloodstream (178). When the body fat is reduced, the excretion rate of lipophilic toxins is enhanced (179).

Xenobiotic and liver conditions that mimic MS

Carbon monoxide (CO) binds to and inhibits CYP450 (84, 92, 180). One half of urban air pollution is attributed to CO (181). Carbon monoxide was dispersed locally from various sources in East Boston and Winthrop, MA (TABLE 1).

Massport 1998 Annual Update Emission Inventory



Acute CO in animals is known to cause:

> segmental empty axonal swelling, dilatation of the extracellular space, swelling and necrosis of astrocytes and oligodendroglia and lamellar separation of myelin sheath predominantly in the deep cerebral white matter. These changes subsided within one week. Instead, collapsed myelin increased in number and phagocytosis of disintegrated myelin was occasionally observed. Astrocytes and oligodendroglias became prominent

> in size and number. Changes suggestive of selective damage of myelin or oligodendroglia were not encountered. (104)

Funata et al. conclude that Wallerian degeneration follows the CO exposure (104).

Acute hepatic failure affects the BBB more with an edema of a cytotoxic type, and less due to increase of vascular permeability. Swelling of the perivascular foot process of astrocytes and dilatation of extracellular spaces were observed in the cerebral cortex, pons, basal ganglia, and cerebellar cortex (182).

El –Fawal et al. report that autoantibodies to CNS substances, along with IgG and astrogliosis have been found in workers of lead and mercury (183).

Conclusion

Age is a factor in both MS and in xenobiotic and heavy metal metabolism. MS is somehow acquired concurrently with the developmental process. Childhood and puberty are years of maturation and rapid growth of the reproductive system, digestive system, immune system and CNS. Myelination is a process of the maturing brain. Children are more vulnerable to xenobiotics because they eat, drink and breathe more than adults and live closer to the ground on which toxic chemicals tend to collect and persist. The young are at greater risk for developing pollutant toxicities (based on animal models) (27) than adults because of developmental processes. The absorption of heavy metals in the GI tract of children is higher than in adults; the young have a greater opportunity for the xenobiotics to reach a toxic site because they have less plasma proteins to bind them to; many of the metabolic routes of excretion, especially Phase 2 conjugation pathways are immature; detoxification enzymes can be immature; the routes of elimination through the bile is lowered by immaturity; the BBB takes years to develop fully, and the young are

left vulnerable to substances that transport into the brain, such as lead. If the toxic substance is of an oxidizing nature, the very young have lower levels of the enzymes, like SOD, and lower plasma vitamin E to act as antioxidants.

However, adults and the elderly can also be at greater risk for toxicity, based on metabolism, enzyme reduction, and basic aging patterns (27). MS may clinically present symptoms at the same stages.

Genetic and environmental factors determine substantial differences among individuals in the metabolism of drugs, carcinogens, and steroid hormones (50). MS is a similarly heterogeneous condition. Xenobiotics were an element of the environment of East Boston and Winthrop, MA, a location that had a predisposing factor or factors to the development of MS.

Prolonged exposure is the decisive factor in toxicity expression, and the closer in proximity to a source, the higher the concentration of exposure to the toxin. The entire MS sample lived near several sources of environmental xenobiotics for the minimum five years to the maximum of forty years; the potential for impact on the CNS is evident.

Unfortunately, assessment of injurious neurological effects of chemicals is quite insufficient (142). Research likely does not fully understand extraordinary burdens on human detoxification systems (184) or at what phase immature systems may be better suited for which xenobiotics. Research does understand that dysfunction of enzyme systems can lead to disease processes (185).

In genetics it has been suggested that “disorders involving modifiers of protein function”, such as enzymes, may do so after the period of childhood and puberty because the homeostatic systems are not completely disrupted by the defects of transcription

factors for enzymes and receptors. The response may be “less congruent with the demands placed on the organism and so become symptomatic more gradually” (185).

When exogenous substances enter the body and bloodstream they must be metabolized, stored or excreted. An analysis of the exposures that East Boston and Winthrop MS patients had, in conjunction with the manner in which the organ systems deal with outside substances that could be harmful at accumulating concentrations, and the manner in which exogenous factors, like nutrients, contribute to the optimal performance of these systems, leaves the possibility that there exists a relationship between heavy metals, chemicals, and the symptomology of MS. It may be that these were the putative environmental agents. If MS is a form of chemical sensitivity, and perhaps pediatric neurotoxicity, then nutritional counseling and protocol should be used to help patients lessen the burden of toxins on cells within the CNS, which may have been previously, and are currently challenged.

Therefore, more investigations of a similar nature as the one conducted for this thesis should be done. A meta-analysis of clusters of MS may be relevant in recognizing a connection between the phenomena of epidemic-like occurrences that may only be caused by environmental factors. Investigations should include other lipophilic toxins which have been introduced into the environment, such as pesticides, industrial waste and emissions from incineration, etc. The possibility exists that multiple sclerosis can be remedied if these new proposals are given consideration.

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APPENDIX 1—Survey

1. Name
2. What is your current age? Please specify
3. What was your age at diagnosis? Please specify
4. Street(s) that you lived on in and for how long?
5. Schools attended and for how many years?

GENETICS

6. What is your ethnicity (e.g. Italian, Irish, Ashkenazi Jew, etc)?
7. Do you have any relative with blonde or red hair?
8. Do you have any relative with blue eyes?
9. Which of these health conditions apply to you? Anxiety, panic, epilepsy, irritable bowel, asthma, allergies, Type I diabetes, Type II diabetes.
10. Do you have any relatives with any of these conditions?

NUTRITION/DIET

11. How often before the age of 16 did you consume: pasta as a meal, bread, cereals, fish and what type, red meat, milk, eggs, fruits and vegetables? (Please specify number of times per week)
12. Were you given a daily multivitamin/mineral supplement as a child?
13. Were you ever given cod liver oil?

TOXINS

14. Besides Logan Airport, do you remember any other source in your environment of heavy metals, hazards or toxins? If yes, please specify.
15. State any occupations you have had since age 16.

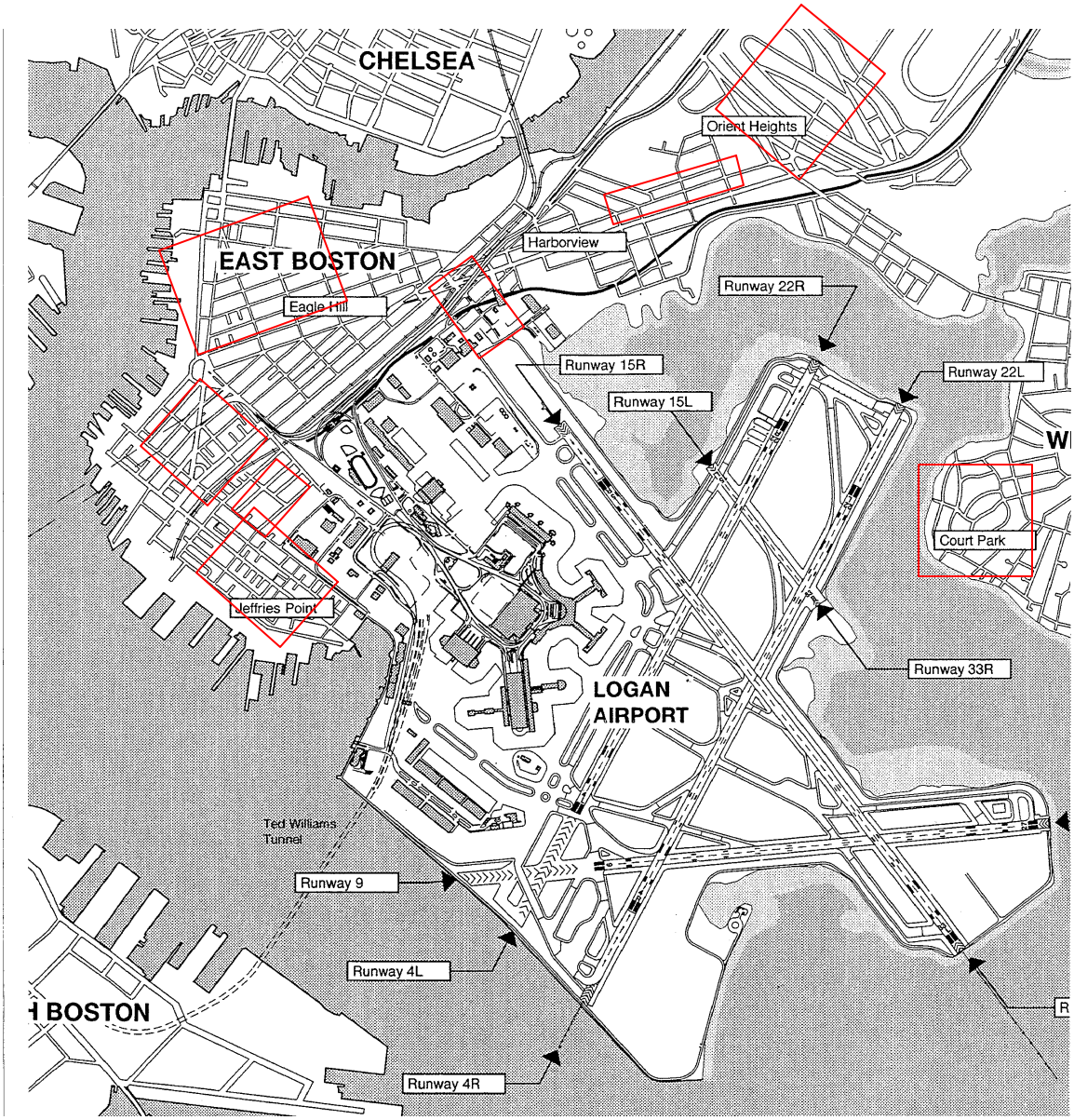
VIRUSES/PATHOGENS

16. Before the age of 20, did you ever have mumps, measles, mononucleosis, or pneumonia?
17. Did you ever receive allergy shots?
18. Did you ever have contact with a dog with canine distemper virus?

TRAUMA OR SURGERY

19. Is there any trauma, e.g. car accident, or major surgery that occurred before age 20 that you feel may have affected your MS? If yes, please specify

APPENDIX 2



(From Boston-Logan International Airport 1997 Annual Update. Pg 5-7, 1998)

= Streets in East Boston and Winthrop on which MS subjects lived and attended schools