

Investigation of Hodgkin's Disease

Among Former Methuen High School Students



Massachusetts Department of Public Health  
Bureau of Environmental Health Assessment

July 2003

## TABLE OF CONTENTS

<b>I.</b>	<b>BACKGROUND.....</b>	<b>1</b>
<b>II.</b>	<b>METHODS .....</b>	<b>2</b>
	<b>A. Case Study of Hodgkin’s Disease.....</b>	<b>3</b>
	<b>a. Develop Study Protocol.....</b>	<b>3</b>
	<b>b. Identify Potentially Eligible Study Population .....</b>	<b>4</b>
	<b>c. Confirmation of Hodgkin’s Disease Among Study Population.....</b>	<b>4</b>
	<b>d. Review of Vital Records.....</b>	<b>4</b>
	<b>d. Participant Contact .....</b>	<b>5</b>
	<b>e. Medical Records .....</b>	<b>5</b>
	<b>f. Questionnaire.....</b>	<b>5</b>
	<b>g. Tissue Samples.....</b>	<b>6</b>
	<b>B. Estimate of Expected Number of Hodgkin’s Disease Cases.....</b>	<b>8</b>
<b>III.</b>	<b>RESULTS .....</b>	<b>11</b>
	<b>A. Case Study .....</b>	<b>11</b>
	<b>a. Participation.....</b>	<b>11</b>
	<b>b. Obtaining Tissue Samples.....</b>	<b>13</b>
	<b>c. Interview.....</b>	<b>13</b>
	<b>B. Expected Versus Observed in Methuen High School .....</b>	<b>18</b>
	<b>C. Hodgkin’s Disease in Methuen as a Whole.....</b>	<b>19</b>
	<b>D. Historical Land Use at Methuen High School.....</b>	<b>20</b>
<b>IV.</b>	<b>DISCUSSION .....</b>	<b>21</b>
	<b>A. Characteristics of Hodgkin’s Disease Participants Relative to the Available Literature and to the HSPH Hodgkin’s Disease Group.....</b>	<b>21</b>
	<b>a. Age, Gender, Race, Ethnicity .....</b>	<b>22</b>
	<b>b. Histology .....</b>	<b>23</b>
	<b>c. Socioeconomic Status and Childhood Environment .....</b>	<b>23</b>
	<b>d. Epstein-Barr Virus .....</b>	<b>25</b>
	<b>e. Possible Occupational/Environmental Risk Factors.....</b>	<b>29</b>
	<b>f. Family History of Cancer.....</b>	<b>29</b>
	<b>B. Estimated Incidence Rate and Hodgkin’s Disease in Methuen as a Whole.....</b>	<b>30</b>
	<b>C. Summary of Characteristics of MDPH Participants and Hodgkin’s Disease in Methuen.....</b>	<b>31</b>
<b>V.</b>	<b>CONCLUSIONS/RECOMMENDATIONS.....</b>	<b>34</b>
	<b>REFERENCES.....</b>	<b>35</b>
	<b>TABLES.....</b>	<b>38</b>
	<b>FIGURES.....</b>	<b>52</b>

Investigation of Hodgkin's Disease  
Among Former Methuen High School Students

I. BACKGROUND

In spring 1995, a local resident of Methuen initially contacted the Methuen Board of Health and requested an investigation of Hodgkin's disease incidence within the community, specifically among former students or graduates of Methuen High School. The Methuen Board of Health then contacted the Massachusetts Department of Public Health, Bureau of Environmental Health Assessment (MDPH/BEHA), for assistance in evaluating these concerns. MDPH/BEHA's first step in responding was the completion of a Phase I evaluation of town-wide Hodgkin's disease incidence rates, using data provided by the MDPH Massachusetts Cancer Registry (MCR). That evaluation indicated that the town overall was not experiencing an unusual incidence of Hodgkin's disease during the period 1982-1990, the most recent period available for review at the time (Purvis, pers. comm., 1995). In addition, Hodgkin's disease was found to be evenly distributed throughout Methuen (Purvis, pers. comm., 1995).

Following this first report, the Methuen BOH then requested that the MDPH/BEHA conduct a more detailed investigation of Hodgkin's disease in light of continuing community concerns, particularly those associated with attending Methuen High School. At that time, MDPH/BEHA staff explained the difficulty of conducting an investigation with a focus on former high school students as Massachusetts does not have a follow-up cancer registry (i.e., the only information available to MDPH/BEHA is the address of an individual at the time of diagnosis).

MDPH/BEHA, however, agreed to move forward with this investigation because the community and the Methuen Board of Health believed all cases of Hodgkin's disease that had occurred among former students or graduates of Methuen High School had been identified, representing a fairly complete cohort.

After additional efforts over the following 1½-2 years to confirm all Hodgkin's disease cases reported by area residents through the MCR, and to estimate an incidence rate in the cohort of students who had attended the high school during the time period of interest, MDPH/BEHA

decided to move forward with follow-up interviews with individuals who had been diagnosed with Hodgkin's disease. MDPH/BEHA believed that this step would best address community concerns and provide better information about the occurrence of Hodgkin's disease in Methuen and any unused patterns that might suggest an association with Methuen High School. Thus, MDPH/BEHA agreed to move forward in late 1997 with efforts to develop a study protocol and to contact individuals that had been identified to us to obtain consent for their participation.

This follow-up investigation aimed to identify the prevalence of known or suspected risk factors among individuals who were students or had graduated from Methuen High School during the period 1979-1993 and who were diagnosed with Hodgkin's disease during the years 1982-1995. The investigation included conducting personal interviews of eligible individuals who agreed to participate; evaluating medical records, and conducting serological and pathologic tissue analyses. The study aimed to learn more about the occurrence of Hodgkin's disease in this group of individuals.

To conduct this work, MDPH/BEHA sought technical assistance from Dr. Nancy Mueller of the Harvard School of Public Health (HSPH), who has conducted extensive research on Hodgkin's disease and is a world-renown expert on the epidemiology of this disease. MDPH/BEHA is grateful to Dr. Mueller for her assistance as well as that of graduate/doctoral student interns working with her and the MDPH.

## II. METHODS

The primary focus of this follow-up investigation was the conduct of personal interviews, collection of biological samples and analysis of the combined information to help learn more about Hodgkin's disease in the cohort of individuals identified previously. In addition, MDPH/BEHA estimated an expected number of Hodgkin's disease cases among students or graduates of Methuen High School during the time period of interest to compare with the observed number of cases. MDPH/BEHA also reviewed available historical land use information for the site where Methuen High School is currently located. Finally, MDPH/BEHA

evaluated the most recently available town-wide cancer incidence data on Hodgkin's disease in Methuen.

#### A. Case Study of Hodgkin's Disease

This section describes the methods for the study of individuals diagnosed with Hodgkin's disease.

##### a. Develop Study Protocol

MDPH/BEHA developed a study protocol (Appendix A) with the assistance of Dr. Mueller and one of her graduate students. The protocol closely mirrored ongoing studies being conducted by Dr. Mueller to enable comparison of data collected for the Methuen individuals with a larger database on Hodgkin's disease patients from the Greater Boston area (i.e., within I-495) under study by Dr. Mueller.

The study protocol was reviewed and approved by the MDPH 24A committee pursuant to the provisions of Massachusetts General Laws, chapter 111, section 24A. Approval for 24A protection was sought to ensure that all personal identifying information collected in this study would be kept strictly confidential in accordance with the laws and regulations of the Commonwealth of Massachusetts relating to confidentiality and privacy, including the provisions of MGL, c. 111, s. 24A, which protects from court subpoena all medical and other personal information collected by the Department as part of this study.

In addition, MDPH/BEHA submitted its study protocol to the MDPH/Lemuel Shattuck Hospital Human Subjects Review Committee for review and approval. This committee is responsible for making sure that risks (if any) to the subject will be outweighed by the potential benefit to the subject and/or to the importance of the information to be gained, that the rights and welfare of each person is adequately protected, and that informed consent will be obtained. The Human Subjects Review Committee approved this study in May 1998 after reviewing the protocol and interviewing the MDPH/BEHA researchers for further details.

b. Identify Potentially Eligible Study Population

The study population of interest was defined as those individuals who were diagnosed with Hodgkin's disease between 1982-1995 and were former students or graduates of Methuen High School between 1979-1993. For this investigation, a case was defined as an individual who had attended or graduated from Methuen High School during the years 1979-1993 during or prior to their Hodgkin's disease diagnosis and whose diagnosis during 1982-1995 was confirmed by the MCR.

In addition, the files of the MDPH Bureau of Health Statistics and Research, Massachusetts Cancer Registry (MCR), were checked for Methuen residents to determine if other individuals who were diagnosed with Hodgkin's disease might fit this case definition that were not included in the original request.

c. Confirmation of Hodgkin's Disease Among Study Population

All names reported to the MDPH/BEHA as having been diagnosed with Hodgkin's disease were checked at the Massachusetts Cancer Registry (MCR) for confirmation of Hodgkin's disease diagnosis. Massachusetts has a population-based cancer registry; regardless of where an individual is diagnosed, his or her actual residence at diagnosed is recorded in the cancer registry file. In 1982, the MCR began collecting information on Massachusetts residents with cancer. All newly diagnosed cancer cases are required by law to be reported to the MCR within six months of the date of diagnosis (M.G.L. c.111s.111B).

d. Review of Vital Records

All cases reported to the MDPH/BEHA were also checked against the death records files at the MDPH Office of Vital Records and Statistics to determine if any reported cases were deceased. If so, information on the death certificate could be used to contact "next-of-kin" of the deceased individual to determine whether the next-of-kin would be willing to participate in the study. Next-of-kin was defined as the individual listed for contact on an individual's death certificate.

#### d. Participant Contact

The Lemuel Shattuck Human Subjects Review Committee required that active physician consent be provided before MDPH/BEHA staff could contact potential participants in the study. Thus, the physicians of record for all eligible individuals, were contacted by letter, explaining the purpose of the study and asking for their active consent for MDPH/BEHA staff to contact their patient. If the physician did not respond to the initial letter, another letter was sent, which was followed by telephone calls until a response was received.

Once the physician provided consent, MDPH/BEHA then wrote a letter to the patient asking to participate in the study. In addition, a detailed consent form was included with the letter to be signed and returned to MDPH/BEHA should the individual agree to participate. If no response was received, a second letter was sent to the individual. If no response to that was received, a certified letter was sent. If the certified receipt was signed and the individual still did not respond, MDPH/BEHA attempted to telephone the individual.

#### e. Medical Records

All participants in the study were asked to provide consent for MDPH/BEHA to request from their physicians a copy of their medical records. The aim of the records review was to confirm diagnostic information and to assess risk factors for Hodgkin's disease as noted in the medical records (e.g., past diagnosis of infectious mononucleosis). Once consent was received from the participant, MDPH/BEHA staff arranged to have the medical records sent to MDPH/BEHA for review and evaluation by a consultant physician.

#### f. Questionnaire

All participants were interviewed using the questionnaire used by Dr. Mueller of the Harvard School of Public Health in her research. The questionnaire focused on gathering information on known risk factors (e.g., number of siblings, maternal education). MDPH/BEHA arranged for a convenient time and location to conduct each of the personal interviews. In addition,

information collected during interviews was supplemented by independent confirmation of certain data (e.g., dates of graduation from Methuen High School).

g. Tissue Samples

All participants were asked to provide consent to have a blood sample taken and allow previous tissue blocks that were available at a diagnosing or treating hospital to be released for specialized analyses. These tissue analyses were for the purpose of determining the presence of specific biomarkers that indicated a history of Epstein Barr viral (EBV) infection. Although EBV infection is extremely common and usually harmless, it is the virus that has been linked most specifically with Hodgkin's disease.

Blood Analyses

The protocol for blood sampling and analysis is contained in the overall study protocol (Appendix A). A trained phlebotomist took blood samples, which were then forwarded to the MDPH State Laboratory Institute in Jamaica Plain, Massachusetts, where it was centrifuged to separate serum. The sera were then sent to Virolab in Berkley, California, for analysis.

All sera of the participants were evaluated for antibody titers (concentrations) to EBV antigens (the viral capsid antigen [VCA], the early antigen [EA], and EB nuclear antigen [EBNA]). Previous studies have shown that patterns of antibodies raised against EBV antigens are altered in Hodgkin's disease patients and provide information regarding an individual's immune status.

Tissue-Block Analyses

The formalin-fixed/paraffin embedded tissue blocks obtained from diagnosing or treating hospitals were shipped to Johns Hopkins Medical School's Oncology Department in Maryland for analysis. Examination of the tissue blocks provided pathological confirmation of case diagnosis and histology type.



Johns Hopkins also analyzed the tissue blocks for the presence of viral genome or viral-encoded proteins (i.e., latent membrane protein 1, or LMP1) or transcript fragments (i.e., abundant small EB encoded nuclear RNA transcripts, or EBER) within the blocks. Identification of EBER, LMP1, or EBNA are considered diagnostic of EBV-associated Hodgkin's disease and individuals so identified are considered to have EBV-positive Hodgkin's disease.

#### h. Comparison with Hodgkin's Disease Patients in HSPH Study

In order to determine whether the Methuen Hodgkin's disease individuals had unusual characteristics or risk factors relative to a larger comparison group of individuals with Hodgkin's disease, their risk factor profiles were compared to those Hodgkin's disease patients in the same age group as the MDPH participants and who were enrolled in a population-based study of Hodgkin's disease in the Greater Boston area that is currently being conducted at the Harvard School of Public Health (HSPH). Data for the comparison between the two groups were taken from the interviews, the blood sample analyses, and the pathologic tissue analyses. A strength of this comparison is that the questionnaire administered to both groups was the same, and the blood and tissue analyses were performed by the same laboratories.

Statistical tests for differences between the two groups of individuals with Hodgkin's disease and calculations of odds ratios (OR), if applicable, were conducted for various known risk factors. The statistical tests include calculation of a "p-value," which helps determine whether the observed difference, if any, may be due to chance. Generally, a p-value less than or equal to 0.05 is considered statistically significant, i.e., the difference is not readily explainable by chance. The OR, also referred to as the relative risk, is a measure of the risk of disease among those exposed to a given factor, relative to the risk of disease among those not exposed.

For the serology, each MDPH participant with serologic data was matched on gender and age (within 1 year) to five randomly selected HSPH cases. The geometric mean antibody titers (GMT) for the matched HSPH cases were then computed for VCA-G, EA (using the higher value of EA-diffuse or EA-restricted components, if both were available), and EBNA. Then, the number of MDPH participants with antibody titers above the GMT value for their matched

HSPH Hodgkin's disease patients was compared with the number of HSPH patients also above the GMT. In addition, the GMTs for each of the EBV antibody groups were calculated for the MDPH and HSPH Hodgkin's disease patients and compared for differences.

#### B. Estimate of Expected Number of Hodgkin's Disease Cases

MDPH/BEHA gathered information from the Methuen School Department and from the MCR to estimate the expected number of Hodgkin's disease cases among Methuen High School students or graduates during the time period of interest. As noted previously, the cohort evaluated here included individuals who attended or graduated from Methuen High School between 1979-1993 and who were diagnosed with Hodgkin's disease during the 1982-1995 period. Statewide cancer incidence data are only available beginning in 1982, and hence, the estimate of the expected number of Hodgkin's disease cases among Methuen High School graduates will be based on the population at the high school beginning in 1982 through 1993. In other words the total population of the school for each and every year during the years 1982-1993 needed to be obtained.

In order to provide a population estimate on which to calculate an expected number of Hodgkin's disease cases, MDPH/BEHA calculated the "person-years" of the student cohort that attended Methuen High School from 1982-1993. These "person-years" were calculated by gender and by age. Because the dates of diagnosis of the participants ranged from 1982-1995, we calculated person-years through 1995 by counting the person years through 1995 of those individuals who were at the high school in 1993.

Information was provided on the number of students in Methuen High School by grade (i.e., 9, 10, 11, and 12) and by gender for each year between and including 1982 through 1993. MDPH/BEHA assumed that students in grade 9 were 15 years old; grade 10, 16 years old; grade 11, 17 years old; and grade 12, 18 years old.

MDPH/BEHA then calculated the statewide incidence rate of Hodgkin's disease by gender and age for the Massachusetts cohort that corresponded to the Methuen High School cohort. The

state population for each year was estimated by calculating mid-year population estimates using 1980, 1990, and 2000 census data to derive estimates of the population by age and gender for each of the years 1982-1995. Using the state data, a crude estimate of the expected number of individuals in the Methuen cohort diagnosed with Hodgkin's disease was calculated using the following general formulas:

- Expected number of individuals diagnosed with Hodgkin's disease = total number of person-years (by age and sex) in cohort x statewide rate of Hodgkin's disease.

The expected number was then compared to the observed number of cases among the Methuen High School cohort. The observed number was divided by the expected number to derive a Standardized Incidence Ratio (SIR). Tests for statistical significance were also conducted (see next section for more explanation on SIRs and statistical tests).

### C. Review of Hodgkin's Disease Incidence in Methuen as a Whole

The final evaluation included an update of previous information on the incidence of Hodgkin's disease in Methuen as a whole. As previously mentioned, MDPH/BEHA had reviewed cancer incidence data from the Massachusetts Cancer Registry in our initial response to concerns about Hodgkin's disease among Methuen High School graduates. These data covered the period 1982-1990. Since then, data through 1999 have become available and are included in this report.

In order to evaluate cancer incidence a statistic known as a standardized incidence ratio (SIR) was calculated. An SIR is an estimate of the occurrence of cancer in a population relative to what might be expected if the population had the same cancer experience as some larger comparison population designated as "normal" or average. Usually, the state as a whole is selected to be the comparison population. Using the state of Massachusetts as a comparison population provides a stable population base for the calculation of incidence rates. As a result of the instability of incidence rates based on small numbers of cases, SIRs were not calculated when fewer than five cases were observed.

Specifically, an SIR is the ratio of the observed number of cancer cases to the expected number of cases multiplied by 100. An SIR of 100 indicates that the number of cancer cases observed in the population evaluated is equal to the number of cancer cases expected in the comparison or “normal” population. An SIR greater than 100 indicates that more cancer cases occurred than expected and an SIR less than 100 indicates that fewer cancer cases occurred than expected. Accordingly, an SIR of 150 is interpreted as 50% more cases than the expected number; an SIR of 90 indicates 10% fewer cases than expected.

Caution should be exercised, however, when interpreting an SIR. The interpretation of an SIR depends on both the size and the stability of the SIR. Two SIRs can have the same size but not the same stability. For example, an SIR of 150 based on 4 expected cases and 6 observed cases indicates a 50% excess in cancer, but the excess is actually only two cases. Conversely, an SIR of 150 based on 400 expected cases and 600 observed cases represents the same 50% excess in cancer, but because the SIR is based upon a greater number of cases, the estimate is more stable. It is very unlikely that 200 excess cases of cancer would occur by chance alone.

To determine if the observed number of cases is significantly different from the expected number or if the difference may be due solely to chance, a 95 percent confidence interval (CI) was calculated for each SIR. A 95 percent CI assesses the magnitude and stability of an SIR. Specifically, a 95 percent CI is the range of estimated SIR values that has a 95 percent probability of including the true SIR for the population. If the 95 percent CI range does not include the value 100, then the study population is significantly different from the comparison or “normal” population. “Significantly different” means there is less than 5 percent chance that the observed difference is the result of random fluctuation in the number of observed cancer cases.

For example, if a confidence interval does not include 100 and the interval is above 100 (e.g., 105-130), then there is statistically significant excess in the number of cancer cases. Similarly, if the confidence interval does not include 100 and the interval is below 100 (e.g., 45-96), then the number of cancer cases is statistically significantly lower than expected. If the confidence interval range includes 100, then the true SIR may be 100, and it cannot be concluded with sufficient confidence that the observed number of cases is not the result of chance and reflects a

real cancer increase or decrease. Statistical significance is not assessed when fewer than five cases are observed.

In addition to the range of the estimates contained in the confidence interval, the width of the confidence interval also reflects the stability of the SIR estimate. For example, a narrow confidence interval (e.g., 103-115) allows a fair level of certainty that the calculated SIR is close to the true SIR for the population. A wide interval (e.g., 85 to 450) leaves considerable doubt about the true SIR, which could be much lower than or much higher than the calculated SIR. This would indicate an unstable statistic.

### III. RESULTS

#### A. Case Study

##### a. Participation

Through reports from Methuen residents and a review of MCR data, MDPH/BEHA identified a total of 14 individuals who were potentially eligible to participate. That is, these individuals were believed to have been diagnosed with Hodgkin's disease during 1982-1995, and were believed to have attended or graduated from Methuen High School during 1979-1993.

Two individuals who were potential Methuen High School graduates had both moved from their address at diagnosis and no forwarding addresses were available. MDPH/BEHA staff searched the Massachusetts Registry of Motor Vehicles address file to see if these individuals could be located. One individual was not located. An address for the second individual was located, but upon attempting to contact this individual to determine whether they may have attended Methuen High School, the mailed envelope was returned indicating that the individual did not currently live at the address and no forwarding information was available. Thus, neither of the two individuals could be included in the study.

Eleven of the twelve remaining individuals were confirmed by the MCR to have been diagnosed with Hodgkin's disease. The one exception was not reported to the MCR for any cancer type or any Massachusetts community of residence. Attempts to gather more information about the individual (e.g., exact address or age at the time of diagnosis) were not fruitful, and hence, this individual could not be included in the study.

Of the remaining 11 individuals, one individual was reported to us as currently attending another school in Methuen at the time of diagnosis. A second individual was reported as having been a former student at the same school but was not reported to us as a former student or graduate of Methuen High School. Although not eligible to participate, MDPH/BEHA agreed to evaluate information from these two individuals that would be analyzed separately from those individuals who had been students at the high school. However, when attempting to contact the physicians of record for permission to contact the patients about the study, one physician noted that his/her patient should not be contacted because of concerns that the physician expressed about the patient's current health status. The physician of record for the second patient reported that they had no record of the individual. Because no physician of record could be located and because the patient did not contact our office directly, this individual could not be included in the interview study.

Of the remaining nine individuals, the physician of record for one individual was no longer in the country, and no other physician of record could be located for the patient. [Note: The MDPH Human Subjects Review Committee requires physician approval prior to contacting a patient unless the individual contacts MDPH directly.] The patient did not contact our office directly, and hence, this individual could not be included in the study. Furthermore, it appeared that this individual may likely have been diagnosed with Hodgkin's disease prior to attending Methuen High School (based on available information on date of birth, date of diagnosis, and date of graduation), and hence, would likely not have been eligible to participate in the study even if physician consent were obtained.

Thus, the final number of eligible individuals was eight. Of these eight individuals, seven consented to participate in the study and one individual refused to participate (see Figure 1). The

dates of graduation of the seven participants ranged from 1979 to 1993, with no two individuals in the same graduating class. Six of the individuals were still living at the time of the study, with the seventh individual deceased. The next of kin of the deceased individual agreed to participate in the study. The six surviving individuals agreed to provide blood samples for analysis, and all seven provided consent for MDPH/BEHA to attempt to obtain tissue blocks from their respective diagnosing or treating hospitals.

b. Obtaining Tissue Samples

Blood samples were obtained from six of the seven eligible study participants (i.e., those surviving) in this study for serology analysis.

MDPH/BEHA attempted to secure tissue block samples from diagnosing or treating hospitals for all seven participants. After extensive efforts, including working with hospitals to locate tissue samples taken more than 15 years prior to this investigation, a total of five tissue block samples were located and sent to Johns Hopkins University for analysis.

c. Interview

The interviews were conducted in person during the summer and fall of 1999. Each interview took approximately 20-30 minutes. With the exception of the proxy interview for the deceased individual, interviews were conducted with the individuals diagnosed with Hodgkin's disease.

The interview answers of all seven MDPH participants were compared to those of 239 HSPH Hodgkin's disease patients. Selection of the HSPH comparison group was based on the ages of the MDPH group. The MDPH participants were all between the ages of 16 and 32 at the time of diagnosis. Thus, all MDPH participants were within the age range typically defined as "young adult" Hodgkin's disease, which corresponds to individuals diagnosed with Hodgkin's disease between the ages of 15-39 years old (Mueller 1996). Therefore, all young adult Hodgkin's disease individuals in the HSPH study (i.e., diagnosed between the ages 15 to 39) were selected for comparison to the MDPH participants.

The risk factor profiles of the two groups are compared in Tables 1 through 7.

### Age at Diagnosis

Table 1 shows the ages at diagnosis of MDPH versus HSPH Hodgkin's disease patients. As noted above, the age at diagnosis of the seven MDPH individuals ranged from the mid-teens to the early 30s, with a mean age of 23 years old. The age distribution of the MDPH participants was similar to the age distribution of the HSPH group. One of the seven MDPH participants was diagnosed while still a student at the high school, while the other six individuals were diagnosed during a period of less than one year to more than 10 years after graduation.

### Gender, Race, and Ethnicity

Table 2 shows the gender distribution in the two groups. Two of the seven MDPH participants were male (29 percent), while about half of the HSPH study participants are male. All seven of the MDPH participants reported their race as white, while 88 percent of HSPH participants are white. One of the seven MDPH participants reported being of Jewish descent.

### Birth Years of Hodgkin's Disease Patients

Table 3 compares the distribution of the birth years of the two groups of Hodgkin's disease patients, a distribution that was similar among the MDPH and HSPH patients (i.e., not statistically significantly different). All seven MDPH participants were born during the period 1960 to 1979, while 87 percent of the HSPH participants were born during this same time period.

### Maternal Education

Table 4 compares the level of maternal education between the two groups. The majority of both groups had mothers who completed at least high school. For example, six of the seven MDPH participants (86 percent) had mothers who completed at least high school, compared with 93 percent for the HSPH group. Four of the seven MDPH mothers completed college (57 percent),



while 42 percent of the HSPH mothers completed at least a college education. Differences between the MDPH and HSPH groups with respect to maternal education were not statistically significant.

#### Number of Siblings

Table 5 shows the number of siblings for each Hodgkin's disease group. The majority of both groups had two or fewer siblings and were similar to each other in terms of the distribution of sibship size among the groups.

#### Housing Density and Ownership

Table 6 shows information on housing density for the MDPH and HSPH participants. All seven of the MDPH participants lived in single-family homes when they were children, while 70 percent of the HSPH participants lived in single-family homes, a difference that was not statistically significant. In addition, all seven MDPH participants lived in homes owned by their own families, while 81 percent of the HSPH participants lived in homes owned by their families, a difference that was not statistically significant.

#### Diagnosis of Infectious Mononucleosis

Table 7 shows how the two groups compared with respect to a prior diagnosis of infectious mononucleosis. The results show similar percentages of participants had a history of this infection (20 percent in the HSPH group and 29 percent, or two of the seven participants, in the MDPH group).

#### Year of Diagnosis

All seven MDPH participants were diagnosed during the 1982-1995 period, with three individuals diagnosed in 1988, two individuals diagnosed in 1995 and one each in 1982 and 1994

(Table 8). Most of the HSPH participants (85 percent) were diagnosed during the 1995-2000 period.

#### Attendance at Nursery School

Table 9 shows that 39 percent (93/236) of the HSPH study group had attended nursery school during childhood, while none of the seven MDPH individuals went to nursery school, a difference that was statistically significant. However, after adjusting for age and gender, history of nursery school was no longer significantly different between the two groups of patients.

#### Family History of Cancer

Table 10 shows that 34 percent (79/234) of the HSPH group had at least one parent diagnosed with cancer, while 71 percent (5/7) of the MDPH group had one parent with cancer. After adjusting for age and gender, parental history of cancer remained statistically significantly more common among the MDPH patients than the HSPH patients.

To further explore this difference, specific sites of cancer were examined. One of the five reported parental cancers in the MDPH group was noted as “skin” cancer, which, if non-melanoma skin cancer, is often excluded in cancer studies (as well as cancer registry databases) due to the high rate of this cancer and the relatively benign nature of non-melanoma skin cancer incidence in the general population. A second cancer type was non-melanoma skin cancer. A third cancer type was reported as “squamous cell carcinoma,” but no primary site was named. Hence, this cancer site was unknown.

The analysis, therefore, was repeated excluding non-melanoma skin or unknown cancers in parents. In both the crude and adjusted analyses, parental history of cancer was no longer statistically significantly different between the two groups of patients. The numbers and proportions of non-skin parental cancers are shown in Table 11.

No MDPH participant reported any sibling who had been diagnosed with cancer.

d. Serology

Results of the serology analyses are shown in Table 12 and Figure 2. Table 12 shows the comparisons between the HSPH and MDPH Hodgkin's disease patients in terms of the number of individuals whose antibody titers (concentrations) were higher than the geometric mean titers (GMT) calculated for the age- and gender-matched HSPH Hodgkin's disease patients. No statistically significant differences were seen between the two groups in terms of the percent of individuals with higher titers than the GMTs. Because antibodies against the early antigen (EA) are frequently undetectable, the number of HSPH versus MDPH patients who had a detectable EA antibody titer was compared, and again, there was no statistically significant difference in the detection of EA between the MDPH individuals and their matched HSPH Hodgkin's disease patients.

Figure 2 illustrates the actual GMT values for the MDPH versus HSPH groups. No statistically significant differences were seen between the GMTs of the two groups for antibody titers against the three EBV antigens shown in the figure.

e. Pathology

The pathologic data of five MDPH cases for whom tissue block data were available were compared to those of 125 HSPH cases aged 15-39 with available pathology results. No statistically significant differences in tumor histology or EBV genome positivity existed between the two groups of patients. Specifically, 66 percent (83/125) of the HSPH cases were of the nodular sclerosis (NS) histology subtype for Hodgkin's disease, while 80 percent (4/5) of the MDPH cases were NS. Eleven percent (14/125) of the HSPH cases were of the mixed cellularity (MC) histology subtype of Hodgkin's disease, while 20 percent (1/5) of the MDPH cases were MC (see Table 13).

Analysis of tissue blocks revealed that eighteen percent (22/122) of the HSPH cases were positive for the EBV genome, while 20 percent (1/5) of the MDPH cases were EBV genome-positive (Table 14).

Of note, prior studies have consistently found that EBV genome-positive Hodgkin's disease cases are more commonly those with MC histology (Jarrett et al. 1996). The single MC case among the MDPH group was also the only EBV genome-positive tumor, in accordance with the usual positive correlation between MC histology and EBV positivity. The remaining four MDPH participants all had NS Hodgkin's disease, and none of the four was positive for EBV genome.

#### B. Expected Versus Observed in Methuen High School

In order to evaluate whether the number of Hodgkin's disease cases reported among Methuen High School students or graduates may have been unusual, MDPH/BEHA estimated an expected number of Hodgkin's disease cases for the cohort of Methuen High School students during the 1982-1995 time period, which corresponds to the time period for which statewide incidence rates are available and during which the reported Methuen cases were diagnosed.

The estimated number of Hodgkin's disease cases during the 1982-1995 period for the population corresponding to the Methuen High School cohort was 4.0 cases. As previously described, eight individuals were confirmed with Hodgkin's disease and reportedly attended or graduated from Methuen High School at the time of or prior to their diagnosis (see Figure 1). Of these eight individuals, two graduated from Methuen High School prior to 1982. Thus, the most reliable observed number of Hodgkin's disease cases during the 1982-1995 period for Methuen High School students or graduates was six.

These estimated expected and observed number of individuals diagnosed with Hodgkin's disease in the Methuen High School cohort result in an estimated SIR of 152, with a 95 percent confidence interval of 52-335. The estimated SIR indicates that more Hodgkin's disease cases occurred among the Methuen High School cohort than expected based on the statewide

experience. However, this difference was not statistically significant when compared with the statewide experience and the confidence intervals were fairly wide.

### C. Hodgkin's Disease in Methuen as a Whole

MDPH/BEHA evaluated cancer incidence data from the Massachusetts Cancer Registry for the period 1990-1995 and 1995-1999, the latest periods available from the MCR. Table 15 shows the incidence data. Also included for comparison purposes are the data for the 1982-1990 period, which had been previously reported to the Methuen BOH and other interested parties. The 1982-1990 data showed that Hodgkin's disease for males and females combined for Methuen was elevated but the elevation was not statistically significant (17 observed versus 13 expected; SIR=130; 95% CI=76-208). The elevation was attributable to an elevation among males that was also not statistically significant (11 observed versus about 7 expected; SIR=161; 95% CI=80-288). Hodgkin's disease among females in Methuen during 1982-1990 occurred about as expected (6 observed versus about 6 expected; SIR=98; 95% CI= 35-210).

For the 1990-1995 period, the number of Methuen residents who were diagnosed with Hodgkin's disease was as expected based on the statewide experience (9 observed versus 8.9 expected; SIR=101). Among males, six individuals were diagnosed with Hodgkin's disease versus about 5 expected. This elevation was not statistically significant (SIR=124; 95% CI=46-272). Three Methuen females were diagnosed with the disease and about four would have been expected based on the statewide experience.

For the 1995-1999 period, there was a statistically significant elevation in Hodgkin's disease among male residents of Methuen, with nine cases observed where about four would have been expected (SIR=224; 95% CI=103-427). Among females during this time period, four individuals were diagnosed with Hodgkin's disease versus about three expected. For the town as a whole, 13 residents were diagnosed with the disease versus about 7 expected (SIR=179; 95% CI=95-305). This elevation for males and females combined was not statistically significant.

Looking more closely at the latest available MCR data for Methuen (1995-1999), two of the 13 individuals diagnosed with Hodgkin's disease during 1995-1999 were children, seven were young adults (defined by Mueller [1996] as 15-39 years old), and four were older adults. The two children, both males, had MC and LP histology, all young adults had NS histology, and three older adults had MC histology. The fourth older adult did not have a specified histology type in the MCR database. Four of the Methuen young adult cases were males and three were females. In terms of year of diagnosis among these 13 individuals, two were diagnosed in each of 1995 and 1996, three in 1997, two in 1998, and four in 1999. The 13 individuals diagnosed with Hodgkin's disease were mapped to address at diagnosis, and the individuals appear widely distributed throughout Methuen.

Among the nine males diagnosed with Hodgkin's disease during 1995-1999, two were children, four were young adults, and three were older adults. The years of diagnosis among these nine males were as follows: two in each of 1995 and 1996, three in 1997, and one in each of 1998 and 1999.

#### D. Historical Land Use at Methuen High School

Construction of Methuen High School was completed and the building was occupied in 1975. In an attempt to determine previous land use at the Methuen High School site, a review of historical Sanborn fire insurance maps was conducted for Methuen. Created originally for the fire insurance industry for risk assessment purposes, Sanborn maps contain highly detailed information on such building features as size and shape, construction details, roof type, occupancy, street addresses, and often date of construction. Sanborn maps for Methuen were reviewed from microfilm copies in the Special Collections department of the State Library of Massachusetts.

Review of the Sanborn maps for Methuen revealed that there did not appear to be a coverage for the specific area of town in which Methuen High School is now located for any Sanborn map dated 1919-1962 (1962 was the latest year available). A possible explanation for the lack of

coverage in this area of Methuen is that there may not have been buildings in the area and hence Sanborn coverages were not needed because there were no buildings to insure.

A 1966 topographic map for the Lawrence Quadrangle (1:24,000 scale), produced by the U.S. Geological Survey, was also reviewed. These maps depict the shape and elevation of the terrain and show and name prominent natural and cultural features, including roads and buildings. No buildings, other than the junior high school, appear in the area where Methuen High School is currently located. The area is depicted as tree-covered land adjacent to Searles Pond and wetlands, although, because of the scale of the map, it is unclear if the wetlands extend into the site now occupied by Methuen High School.

In summary, review of available material suggests that the Methuen High School site was unoccupied land prior to its construction, which was completed in 1975 for occupancy.

#### IV. DISCUSSION

This investigation comprised four types of evaluations: (1) an interview study (with accompanying serological and tissue analyses) of former students or graduates of Methuen High School who had been diagnosed with Hodgkin's disease using a well-established large scale local study population for comparison; (2) estimating the expected versus observed number of Hodgkin's disease among the cohort of Methuen High School students for the time period of interest; (3) an update on the incidence of Hodgkin's disease for Methuen as a whole; and (4) a review of available information on historical land use at the Methuen High School site. The results of information gathered during this investigation are discussed in the context of the latest available information about Hodgkin's disease from the scientific literature.

##### A. Characteristics of Hodgkin's Disease Participants Relative to the Available Literature and to the HSPH Hodgkin's Disease Group

Hodgkin's disease (or Hodgkin's lymphoma) is a form of cancer that involves the lymphatic system. The disease accounts for less than 1 percent of all cancer types (ACS 2001). Reviews of

national and Connecticut tumor registry data indicate that more recently, Hodgkin's disease incidence has increased among young adults and was greater for women (Mueller 1999). The clinical and cellular features of Hodgkin's disease suggest a chronic infectious process is associated with Hodgkin's disease, making this cancer an exception from what is generally known of cancer (Mueller 1996).

a. Age, Gender, Race, Ethnicity

A distinguishing feature of Hodgkin's disease is its bimodal age incidence. In economically advantaged countries, few cases occur among children, followed by a rapid increase among teenagers peaking at about age 25. Incidence then decreases to a plateau through middle age, after which incidence increases again with increasing age (Mueller 1996). In developing countries, two incidence peaks occur in childhood and older adult age groups (Jarrett and MacKenzie 1999). The bimodal age distribution of this disease suggests that distinct etiologies (or causes) for Hodgkin's disease may be involved for each group. MacMahon was the first to recognize the bimodality in age-related incidence of Hodgkin's disease and suggested that the young adult form of the disease may be the result of an infection process (Mueller 1999).

The disease occurs more often among males than females, but gender differences are less marked among young adult Hodgkin's disease cases (Jarrett and MacKenzie 1999). The disease occurs more often among whites than among blacks (Mueller 1996), and being of Jewish descent increases an individual's risk (Mueller 1999).

Among the MDPH Hodgkin's disease interview participants, five of the seven individuals were female. All reported being white. One participant reported being of Jewish descent. All MDPH participants were diagnosed in the age range defined by Mueller (1996) as young adults, i.e., 15-39 years of age. The mean age at diagnosis among this group was 23 years old, near the peak age for Hodgkin's disease among young adults (i.e., about 25 years of age).

The eighth eligible individual, who refused participation, was a male. Hence the gender distribution among the eight eligible participants was five females and three males, which is



somewhat consistent with the literature that reports that young adult Hodgkin's disease occurs about equally between the genders.

b. Histology

Hodgkin's disease has four major histological subtypes: lymphocytic predominance (LP); nodular sclerosis (NS); mixed cellularity (MC); and lymphocyte depletion (LD) (Mueller 1996). NS Hodgkin's disease is the predominant histology in the young adult age group, while MC Hodgkin's disease is relatively more frequent in children and older adults (Jarrett and MacKenzie 1999).

Among the MDPH Hodgkin's disease participants, who were all young adults when diagnosed, six of seven had NS Hodgkin's disease, while the seventh had MC Hodgkin's disease, a distribution consistent with the literature. A somewhat similar distribution was seen with the HSPH study group, with NS Hodgkin's disease occurring in two-thirds of these individuals.

c. Socioeconomic Status and Childhood Environment

Hodgkin's disease trends in the young adult population reveal that the disease has become increasingly associated with populations both of middle to higher socioeconomic status (e.g., higher education, less crowded housing), small family size, and early birth order (Mueller 1996). The association between socioeconomic status and Hodgkin's disease appears to be specific to the NS subtype among young adults (Mueller 1999). These factors are consistent with susceptibility to late infections with common childhood viruses, supporting the theory that Hodgkin's disease is associated with an infectious agent (Mueller 1999). In contrast, among children and older adult patients, a negative association with social class has been described (Jarrett and MacKenzie 1999).

In the MDPH participant group, all of whom were young adults, all seven participants lived in single-family housing that was owned by their families when they were children. In addition, the majority of participants had mothers who completed a college education (four of the seven

participants). The maternal education and single-family housing characteristics of the MDPH group were somewhat similar to the HSPH group.

Also, the majority of MDPH participants had two or fewer siblings, which was similar to the HSPH group. Sibship has been identified as an important factor in previous studies in that children with no or few siblings do not develop immunity as strongly as children with larger numbers of siblings.

With respect to birth order, three of the seven MDPH participants were first-born children, and an additional three individuals were either second- or third-born children. At the time of this analysis, no comparison with the HSPH group was available with respect to birth order. Previous studies have shown a higher risk of Hodgkin's disease among first through third birth order relative to fourth birth order or later (Gutensohn and Cole 1981).

When compared with the HSPH Hodgkin's disease group, socioeconomic status and childhood environment characteristics were not significantly different among the two groups, indicating that these two groups are similar with respect to characteristics that have been associated with increased young adult Hodgkin's disease risk in previous studies. However, in the current population-based HSPH study, these classic risk factors have not been found to be associated with increased Hodgkin's disease risk, possibly reflecting changes in social behavior during recent decades. For example, attendance at nursery school appears to be protective, possibly reducing the role of family structure or other determinants of childhood environment on Hodgkin's disease risk (Chang, pers. comm., 2002). In the 1960s, only about 5 percent of children attended nursery school, while about 50 percent attended nursery schools in the 1990s. Attendance at nursery schools would presumably increase the likelihood of earlier exposures to common childhood viruses, thereby reducing the risk of subsequent development of young adult Hodgkin's disease. Interestingly, none of the seven MDPH participants reported attending nursery school.

MDPH/BEHA also compared readily available information on socioeconomic status (SES) indicators among the MDPH study participants versus Methuen as a whole to see if the study

participant characteristics might differ from Methuen as a whole. Information on Methuen as a whole was taken from the 1970 and 1980 censuses, given that the Methuen participants were children primarily during the 1970s and 1980s.

All seven MDPH participants reported living in homes owned by their families, versus 65.9 percent of the 1970 and 73.4 percent of the 1980 Methuen populations reporting they lived in owner-occupied housing. All seven MDPH participants lived in single-family homes. For Methuen as a whole, 59.8 percent of housing units were single-family homes according to the 1970 census, and for the 1980 census, 68.7 percent were single-family homes.

Six of the seven (86 percent) MDPH participants had mothers who completed at least a high school education. For Methuen as a whole, the percent of women/mothers who completed high school or college educations in 1970 was 53.6 percent and in 1980, 67.4 percent.

The comparison of MDPH participants versus readily available socioeconomic status indicator information for Methuen as a whole suggests that the MDPH participants may have had higher SES indicators, consistent with risk factor information for young adult Hodgkin's disease and that this group of individuals may have been at somewhat higher risk than the general population of Methuen.

#### d. Epstein-Barr Virus

The association between Epstein-Barr virus (EBV) and Hodgkin's disease is now well established (Mueller 1996, 1999; Jarrett and MacKenzie 1999; Weiss 2000). EBV is a herpes virus and has a widespread distribution throughout the world with more than 80 percent of healthy adults infected by the third decade of life (Jarrett and MacKenzie 1999). Primary infection is usually asymptomatic but when infection is delayed until adolescence, as is frequent in developed countries, EBV causes infectious mononucleosis in about 50 percent of cases (Jarrett and MacKenzie 1999).

Although the association between EBV and Hodgkin's disease is well established, only a proportion of cases are EBV positive in the tumor cells. EBV positivity is strongly associated with histology subtype of Hodgkin's disease (Jarrett and MacKenzie 1999; Weiss 2000). About 70 percent of Hodgkin's disease patients with MC or LD histology are EBV-positive, while less than 20 percent of individuals with NS histology are EBV-positive (Weiss 2000). Age at diagnosis and EBV-positivity are also associated (Jarrett and MacKenzie 1999). Children and older adults are more likely to be EBV-positive than young adults (Jarrett and MacKenzie 1999). Among children, EBV-associated rates are generally higher for patients aged less than 10 years (Jarrett and MacKenzie 1999; Weiss 2000). The lowest proportion of EBV-positive cases are found among young adults with NS Hodgkin's disease.

On the basis of what is known about Hodgkin's disease epidemiology, Jarrett and MacKenzie (1999) proposed the following model for three distinct entities of Hodgkin's disease based on age at diagnosis and EBV-positivity. The first entity is EBV-positive and has a peak incidence below the age of 10 years. It is mainly MC Hodgkin's disease with more males than females and a higher incidence in developing countries with less favorable socioeconomic conditions. The second entity affects primarily older adults and is also EBV-positive, mainly MC Hodgkin's disease, and has a higher male/female ratio. The third type accounts for the young adult age incidence peak. Among these individuals, the disease is usually EBV-negative, NS Hodgkin's disease, affects males and females equally, and is associated with a high standard of living in childhood (Jarrett and MacKenzie 1999).

In addition, several studies have shown an association between Hodgkin's disease and a prior diagnosis of infectious mononucleosis (IM) as well as elevated antibody titers against EBV antigens (Jarrett and MacKenzie 1999). The association of Hodgkin's disease and IM appears primarily among young adult patients (Jarrett and MacKenzie 1999, Hjalgrim et al. 2000). For example, a recent study found a threefold increased risk of Hodgkin's disease in young adults with a prior diagnosis of IM (Hjalgrim et al. 2000).

Numerous studies have also shown that Hodgkin's disease patients as a group differ from controls in having elevated titers (concentrations) against the EBV antigens, VCA and EA,

which indicates viral activation (Mueller 1999). In cohort studies that have measured antibodies to these EBV antigens, elevated titers to VCA and EA, as well as EBNA, were observed prior to diagnosis with Hodgkin's disease, thereby predictive of subsequent development of the disease (Mueller 1999). When considering serology results, it should be noted that host control of latent (or dormant) Epstein-Barr virus infections is primarily by the virus-specific cytotoxic T cells, not the antibodies. The relative level of specific antibodies appears to reflect the level of viral antigen (Mueller 1999).

Available evidence indicates that if a patient has Hodgkin's disease, the likelihood that the tumor itself tests positive for EBV genes or gene products appears to be related to factors indicative of somewhat poorer host response: namely, male sex, living under somewhat poorer conditions, and having mixed cellularity histology (Mueller 1999).

Although there is an association between elevated antibody titers to EBV antigens among Hodgkin's disease patients, the evidence is not conclusive to show that individuals with elevated titers are more or less likely to be EBV-positive (Jarrett and MacKenzie 1999, Mueller 1999). Likewise, the association between prior history of infectious mononucleosis and EBV-positivity is not clear (Jarrett and MacKenzie 1999).

Clearly, EBV-negative Hodgkin's disease occurs, particularly among young adult NS Hodgkin's disease patients. It is thought that perhaps another infectious agent that has yet to be identified may be associated with EBV-negative Hodgkin's disease (Weiss 2000; Jarrett and MacKenzie 1999). As noted previously, NS Hodgkin's disease is most common among young adults and young adult Hodgkin's disease is the most strongly associated with a sheltered childhood environment, i.e., delayed childhood infection. In addition, the risk for Hodgkin's disease among those with a prior diagnosis of infectious mononucleosis is higher among young adults than other age groups (Hjalgrim et al. 2000). An alternative hypothesis for EBV-negative Hodgkin's disease is that EBV is involved in the etiology of essentially all Hodgkin's disease cases, but the viral genome itself is somehow lost from the tumor cells in patients with a stronger host response (Mueller 1999).

In summary, there is substantial evidence that age at infection, immune function, and EBV is central to the etiology of Hodgkin's disease (Mueller 1999). However, many questions remain about EBV negative Hodgkin's disease, and the relation of the individual risk factors and serology status to the EBV-positive status has yet to be understood (Mueller 1999).

In the case of the MDPH Hodgkin's disease patients, five tissue block samples were available for analysis by Johns Hopkins researchers. Four of the five MDPH Hodgkin's disease participants had the NS histology subtype. One individual had the MC subtype (confirmed through tissue analysis and medical records review). Consistent with the literature, the individual with the MC subtype had EBV-genome positivity in the tissue analysis, while none of the four NS tissues available for analysis had EBV-genome positivity.

It should also be noted that for the two individuals who participated in our study but for whom tissue blocks could not be obtained, a review of their medical records revealed that they had NS Hodgkin's disease. Thus, of the seven MDPH young adult participants, six had NS Hodgkin's disease, a distribution consistent with the literature. Among the seven participants, two reported a diagnosis of infectious mononucleosis, both occurring less than 10 years prior to their Hodgkin's disease diagnosis.

The serology analyses indicate that the antibody titers of the MDPH participants did not differ significantly from the HSPH Hodgkin's disease group. Although there was no healthy young adult group to compare serology results with, previous studies have indicated elevated titers against EBV antibodies among young adult Hodgkin's disease patients (Mueller 1996). Thus, the fact that the MDPH titers were similar to the HSPH Hodgkin's disease group indicated that the MDPH group likely had elevated levels relative to a healthy population. Furthermore, two of the seven MDPH individuals had serology results that suggested that previously "latent" (or dormant) EBV infection had become reactivated. This reactivation may have played a role or indicated increased risk in the subsequent development of Hodgkin's disease.

e. Possible Occupational/Environmental Risk Factors

Occupational exposures to workers in the chemical industry, to herbicides, and to woodworkers have also been suggested in several epidemiologic studies to be associated with the development of Hodgkin's disease (Mueller 1999). However, specific chemical exposures related to the development of this disease have not been identified and results of studies investigating occupational exposures are inconsistent (Mueller, 1999).

MDPH/BEHA reviewed the interview responses of all participants with respect to occupational history. One of the seven MDPH participants reported an occupation that has been associated with Hodgkin's disease.

f. Family History of Cancer

Mueller (1996) summarized literature on the possible role of genetics in Hodgkin's disease. Some studies that examined the subsequent occurrence of Hodgkin's disease among siblings to one already diagnosed with the disease found that siblings of a young adult with Hodgkin's disease have a higher risk of developing the disease than do members of the general population. In addition, siblings of the same gender as the one with Hodgkin's disease were at higher risk than opposite-gender siblings (Mueller 1996). This phenomenon is also seen in other diseases that involve immune dysfunction and that are also suspected of viral etiologies (causes): multiple sclerosis, sarcoidosis, and Bechet's disease (Mueller 1996). This phenomenon also may not necessarily reflect solely a genetic role because childhood environmental exposures are more likely to be similar for siblings of the same gender (Mueller 1996). Studies by Mack et al. (as cited in Mueller 1999) found a strong increased risk of Hodgkin's disease among identical twins, but no increased risk among fraternal twins, arguing for a genetic basis for susceptibility to the disease (Mueller 1999). Other studies of multi-case family occurrences of Hodgkin's disease (including among siblings and cousins) provide other evidence of genetic factors that are associated with immune competence, which then plays a role in the development of Hodgkin's disease (Mueller 1996). For example, Chakravarti et al. (1986) found evidence of a recessive susceptibility gene that was tightly linked to the human leukocyte antigen (HLA) complex.

A recent study (Grufferman et al. 1998) found statistically significant excesses of cancer in families of individuals with Hodgkin's disease, which may suggest some genetic role. The types of cancer in excess were Hodgkin's disease, melanoma, testicular, lympho-reticular, and perhaps, premenopausal breast cancer (Grufferman et al. 1998).

Among the MDPH participants, no sibling was reported with any type of cancer. The occurrence of cancers among parents (excluding non-melanoma skin and unknown cancers) of the MDPH participants versus the HSPH participants was not statistically significantly different between the two groups. One MDPH participant reported a parent diagnosed with a type of cancer that has been suggested to be part of a group of cancers found in families of individuals with Hodgkin's disease.

#### B. Estimated Incidence Rate and Hodgkin's Disease in Methuen as a Whole

The estimated incidence rate of Hodgkin's disease among the cohort of Methuen High School students evaluated in this study indicated that more cases of Hodgkin's disease occurred than would have been expected based on the statewide Hodgkin's disease experience. However, the elevation was not statistically significant and the confidence intervals were fairly wide.

A review of MCR data for Methuen as a whole showed an elevation during the 1982-1990 period that was not statistically significant. Data from 1990-1995 indicated that town-wide, Hodgkin's disease occurred about as expected in Methuen. The latest available data from the MCR for 1995-1996 indicated a statistically significant elevation in Hodgkin's disease among males, with Hodgkin's disease occurring about as expected for females in Methuen as a whole. Review of the age distribution and histology subtypes for current Methuen male residents diagnosed with Hodgkin's disease revealed that two were children, four young adults, and three older adults, with each age category having histology consistent with that age category. Thus, the age and histology pattern among these males was consistent with the scientific literature on Hodgkin's disease. Review of the geographic distribution for these individuals based on address at diagnosis did not reveal any unusual geographic concentration within Methuen. Finally, the



years of diagnosis among these nine males were fairly evenly spread out during the 1995-1999 period.

### C. Summary of Characteristics of MDPH Participants and Hodgkin's Disease in Methuen

Overall, of the original 14 individuals initially identified as potentially eligible to participate in this follow-up evaluation, eight were located, were reportedly students or graduates at Methuen High School at the time of or prior to diagnosis and during the time period of interest, and were confirmed by the MCR as having been diagnosed with Hodgkin's disease. Seven of these eight individuals agreed to participate in the MDPH interview study that also included analysis of blood and tissue block data.

Evaluation of interview, serology, and tissue block data indicated that the MDPH participants had generally similar Hodgkin's disease risk factor profiles as did a larger comparison group of Hodgkin's disease patients from the Greater Boston area under study by the Harvard School of Public Health. The MDPH participants had socioeconomic and childhood environment characteristics that have been shown previously to be risk factors for Hodgkin's disease, particularly young adult Hodgkin's disease (e.g., single-family and owner-occupied homes; small family size and early birth order; high maternal education). In addition, the MDPH participants showed somewhat higher socioeconomic indicators than Methuen as a whole during their childhood, suggesting that this group was at somewhat higher risk of Hodgkin's disease than the general Methuen population. These socioeconomic and childhood environment characteristics are thought to reflect a greater likelihood of later infection to common childhood viruses, such as the EBV, which in turn is thought to be a risk factor for subsequent development of young adult Hodgkin's disease. Other risk factors, such as prior diagnosis of infectious mononucleosis (in two participants) and an occupation that has been associated in some studies with Hodgkin's disease (in a third participant), were also present among the MDPH group.

Review of the histology of the seven participants also showed a pattern consistent with the literature in that most of these young adults were diagnosed with the NS subtype of Hodgkin's

disease, the most common histology subtype among this age group. The serology analyses showed similar titers (concentrations) of antibodies to EBV antigens as was seen in the HSPH group, again indicating that the MDPH participants were not unusual in terms of what has been measured among a larger group of young adults from the Greater Boston area diagnosed with Hodgkin's disease. Analysis of tissue blocks for the presence of EBV genome revealed that one MDPH participant was EBV-positive and, notably, that individual had the MC subtype of Hodgkin's disease in which EBV-positivity is most strongly associated.

Most of the MDPH participants were EBV-negative (as determined through tissue block analysis). This finding is consistent with the literature, which indicates that young adult NS Hodgkin's disease is usually EBV-negative. It does appear, however, that some sort of infectious process still plays a role in young adult EBV-negative Hodgkin's disease (Mueller 1996, 1999; Weiss 2000; Jarett and MacKenzie 1999), as Hodgkin's disease among this age group is most strongly associated with a sheltered childhood environment, i.e., delayed childhood infection, and the risk for Hodgkin's disease among those with prior diagnosis of infectious mononucleosis are higher among young adults than other age groups (Hjalgrim et al. 2000).

MDPH attempted to determine quantitatively whether the number of Hodgkin's disease cases that occurred among the Methuen High School cohort during the time period of interest may have been unusually high based on the statewide experience. The resulting estimate indicated that Hodgkin's disease was elevated in this group but the elevation was not statistically significant.

A review of Hodgkin's disease in Methuen as a whole showed an elevation in Hodgkin's disease during the 1982-1990 period, but the elevation was not statistically significant. Hodgkin's disease occurred about as expected during 1990-1995, but then was statistically significantly elevated among males during 1995-1999. A detailed review of available information from the MCR for the 1995-1999 time period indicated that the age distribution was somewhat spread out among three age groups (2 cases in children, 4 in young adults, and 3 in older adults) and that each age group had individuals with the histology type most commonly seen in that age group

according to the scientific literature. Furthermore, the years of diagnosis were somewhat evenly spread across the 1995-1999 time period, suggesting that there was not a concentration of diagnoses in any particular year. Finally, MDPH staff mapped the residences of diagnosis for all individuals diagnosed with Hodgkin's disease in Methuen during 1995-1999, and the geographic distribution was fairly even throughout Methuen.

MDPH also reviewed available information on historical land use in the area where Methuen High School is located. This information suggests that prior to 1975, when the school was completed and occupied, the land did not have other buildings and was a wooded tract lying to the north of a pond and wetlands. Thus, there was no evidence of previous environmental contamination on the site.

All of the information reviewed in this investigation therefore suggests that the pattern of Hodgkin's disease seen among this group of former students or graduates of Methuen High School does not appear unusual in terms of risk factor characteristics that have been linked with Hodgkin's disease risk among young adults. The seven MDPH participants were not remarkably different from the 239 HSPH cases that served as a representative group of young adult Hodgkin's disease patients from the Greater Boston area. No two MDPH interview participants were believed to be members of the same Methuen High School graduating class, with graduation dates varying over the time period 1979-1993. There did not appear to be a temporal pattern with respect to date of diagnosis and attendance at the high school. For example, the interview participants who were diagnosed in the same year as other participants (e.g., three participants were diagnosed in 1988) did not all attend Methuen High School at the same time.

Mueller (1996, 1999) reviewed evidence for "clustering" or "aggregation of exposure" of Hodgkin's disease (e.g., among high school populations) that might be attributable to Hodgkin's disease being a contagious disease that could be transmitted by person-to-person contact.

[Clustering refers to concentration of cases in time and place at the time of diagnosis.

Aggregation of exposure refers to possible shared causal exposures with diagnoses occurring later at different times and /or places (Mueller 1999)]. Mueller concluded that on balance there is little to support these hypotheses (Mueller 1996, 1999). She also noted this fact is not

inconsistent with Hodgkin's disease having an infectious cause. That is, a disease can be initiated by an infection but may not itself be transmitted by person-to-person contact (Mueller 1996).

## V. CONCLUSIONS/RECOMMENDATIONS

Information reviewed in this report did not indicate that attending Methuen High School is likely to play a primary role in the pattern of Hodgkin's disease occurrence among former students or graduates of the high school. Thus, MDPH/BEHA does not recommend further evaluation of Hodgkin's disease among Methuen High School students or graduates at this time.

MDPH/BEHA will continue to monitor Hodgkin's disease incidence in Methuen through the Massachusetts Cancer Registry.

## REFERENCES

Alexander F.E., R.F. Jarrett, D. Lawrence, A.A. Armstrong, J. Freeland, D.A. Gokhale, E. Kane, G.M. Taylor, D.H. Wright and R.A. Cartwright. 2000. Risk factors for Hodgkin's disease by Epstein-Barr virus (EBV) status: prior infection by EBV and other agents. *British Journal of Cancer* 82(5): 1117-1121.

American Cancer Society. 2001. *Cancer Facts & Figures 2001*. Atlanta: American Cancer Society, Inc.

American Cancer Society. 1999. Hodgkin's Disease. Available at:  
<http://www3.cancer.org/cancerinfo/>.

Chang, E. 2002. Personal communication (e-mail from Ellen Ching, Harvard School of Public Health, to Martha Steele, Massachusetts Department of Public Health, December 2002).

Chakravarti, A., S.L. Halloran, S.J. Bale, and M.A. Tucker. 1986. Etiological heterogeneity in Hodgkin's disease : HLA linked and unlinked determinants of susceptibility independent of histological concordance. *Genetic Epidemiol.* 3:407.

Grufferman, S., R.F. Ambinder, Y.Y. Shugast, M.L. Brecher, and G.S. Gilchrist. 1998. Increased cancer risk in families of children with Hodgkin's disease. *Am. J. Epidemiol.* 147(11):S8.

Gutensohn (Mueller), N., and P. Cole. 1977. Epidemiology of Hodgkin's disease in the young. *Int. J. Ca* 19:595-604.

Gutensohn (Mueller), N., and P. Cole. 1981. Childhood social environment and Hodgkin's disease. *New England Journal of Medicine* 304:135-140.

Harvard. 1996. Harvard Report on Cancer Prevention, Volume 1. Causes of Human Cancer: Infectious agents. *Cancer Causes and Control*, 1996, 7(8):S25-27.

Hjalgrim H. J. Askling, P. Sorensen, M. Madsen, N. Rosdahl, H.H. Storm, S. Hamilton-Dutoit, L. Stener Eriksen, M. Frisch, A. Ekbom, and M. Melbye. 2000. Risk of Hodgkin's disease and other cancers after infectious mononucleosis. *Journal of National Cancer Institute*. 92(18).

Jarrett, R.F., and J. MacKenzie. 1999. Epstein-Barr Virus and other candidate viruses in the pathogenesis of Hodgkin's disease. *Seminars in Hematology*. 36(3):260-269.

Kosary, C.L., L.A.G. Ries, B.A. Miller, B.F. Hankey, A. Harris, and B.K. Edwards (eds). 1995. SEER Cancer Statistics Review, 1973-1991. Tables and Graphs, National Cancer Institute. NIH Publication No. 96-2789. Bethesda, MD.

Mueller, N.E. and S. Grufferman. 1999. The epidemiology of Hodgkin's disease. In: Hodgkin's Disease (eds. P.M. Mauch, J.O. Armitage, V. Diehl, R.T. Hoppe, and L.M. Weiss) Lippincott, Williams Wilkins, Philadelphia, PA.

Mueller, Nancy E. Hodgkin's Disease. In: *Cancer Epidemiology and Prevention*. 2<sup>nd</sup> Ed, edited by Schottenfeld D, Fraumeni. JF. New York: Oxford University Press: 1996.

Mueller, Nancy E, A. Evans, N.L. Harris, G.W. Comstock, E. Jellum, K. Magnus, N Orentreich, F. Polk, and J. Vogelman. 1989. Hodgkin's disease and Epstein-Barr Virus. Altered antibody pattern before diagnosis. *New England Journal of Medicine* 320:689-695.

Purvis, J. 1995. Personal communication (letter to Pamela Bachrach, Methuen Director of Public Health, from Jeffrey Purvis, Massachusetts, Department of Public Health, Bureau of Environmental Health Assessment, dated June 20, 1995). Boston, MA.

Steckman B.G., P.M. Mauch, R.F. Ambinder, R. Mann, G.S. Pinkus, M.E. Kadin, B. Sherburne, A. Perez-Atayde, I. Thior and N. Mueller. 1998. Epstein-Barr virus in Hodgkin's disease:

correlation of risk factors and disease characteristics with molecular evidence of viral infection. *Cancer Epidemiology, Biomarkers & Prevention*. 7: 1117-1121.

Weiss LM. 2000. Epstein-Barr virus and Hodgkin's disease. *Curr Oncol Rep* 2(2):199-204.

## TABLES

Table 1: Age at Diagnosis: MDPH and HSPH Hodgkin's Disease Participants

Age group	HSPH	MDPH
15-19	23 (10%)	2 (29%)
20-24	53 (22%)	2 (29%)
25-29	54 (23%)	2 (29%)
30-34	60 (25%)	1 (14%)
35-39	49 (20%)	0 (0%)
Total	239	7

p=0.36



Table 2: Gender Distribution of MDPH and HSPH  
Hodgkin's Disease Participants

Gender	HSPH	MDPH
Male	118 (49%)	2 (29%)
Female	121 (51%)	5 (71%)
Total	239	7

OR=2.4, p=0.28

Table 3: Year of Birth of MDPH and HSPH Hodgkin's Disease Participants

Birth year	HSPH	MDPH
1940-1949	2 (1%)	0 (0%)
1950-1959	18 (7%)	0 (0%)
1960-1969	121 (51%)	5 (71%)
1970-1979	85 (36%)	2 (29%)
1980+	13 (5%)	0 (0%)
Total	239	7

p=0.80

Table 4: Maternal education for MDPH and HSPH Hodgkin's Disease Patients

Educ. Level	HSPH	MDPH
Below H.S.	16 (7%)	1 (14%)
High school	122 (51%)	2 (29%)
College	79 (33%)	4 (57%)
Beyond college	22 (9%)	0 (0%)
Total	239	7

p=0.38

Table 5: Sibship Size in MDPH and HSPH Hodgkin's Disease Patients

No. of sibs	HSPH	MDPH
0	10 (4%)	0 (0%)
1	75 (31%)	3 (43%)
2	74 (31%)	1 (14%)
3+	80 (33%)	3 (43%)
Total	239	7

p=0.71

Table 6: Housing Density in MDPH and HSPH

(1) Hodgkin's Disease Patients

Home type	HSPH	MDPH
1-family	167 (70%)	7 (100%)
2-family	36 (15)	0 (0%)
3-family	11 (5%)	0 (0%)
4+ families	18 (7%)	0 (0%)
Other	7 (3%)	0 (0%)
Total	239	7

p=0.56

Table 7: History of Infectious Mononucleosis  
 In MDPH and HSPH Hodgkin's Disease Patients

IM history	HSPH	MDPH
Yes	47 (20%)	2 (29%)
No	187 (80%)	5 (71%)
Total	234	7

OR=0.63, p=0.58

Table 8: Year of Diagnosis of MDPH and HSPH Hodgkin's Disease Patients

Dx period	HSPH	MDPH
<1980	2 (1%)	0 (0%)
1980-1984	5 (2%)	1 (14%)
1985-1989	15 (6%)	3 (43%)
1990-1994	13 (5%)	1 (14%)
1995-1999	185 (77%)	2 (29%)
2000+	19 (8%)	0 (0%)
Total	239	7

p<0.0001

Table 9: Nursery School in Childhood For MDPH and HSPH Patients

Nursery school	HSPH	MDPH
Yes	93 (39%)	0 (0%)
No	143 (61%)	7 (7%)
Total	150	93

p=0.034



Table 10: Parental Cancer Among MDPH and HSPH Patients

Parent cancer	HSPH	MDPH
Yes	79 (34%)	5 (71%)
No	155 (66%)	2 (29%)
Total	234	7
	OR=0.20, p=0.039	

Table 11: Non-skin Parental Cancer For MDPH and HSPH Hodgkin's Disease Patients

Parent cancer	HSPH	MDPH
Yes	59 (25%)	2 (29%)
No	175 (75%)	5 (71%)
Total	234	7

OR=0.84, p=0.84

Table 12: Prevalence of Elevated Titers of Antibodies Against Epstein-Barr Antigens Among MDPH and HSPH Hodgkin's Disease Patients

Antibody titer above GMT	HSPH	MDPH	Total	p-value
VCA-G	17/30 (57%)	3/6 (50%)	20/36	0.76
EA	14/30 (47%)	2/6 (33%)	16/36	0.55
EA (Y vs. N)	18/30 (60%)	2/6 (33%)	20/36	0.23
EBNA	18/30 (60%)	5/6 (83%)	23/36	0.28

GMT (geometric mean titer) determined from gender- and age-matched HSPH patients to the MDPH patients..

VCA = viral capsid antigen

EA = early antigen

EBNA = Epstein Barr nuclear antigen

Table 13: Histologic Subtype of Hodgkin's Disease Among MDPH and HSPH Participants

Histology	HSPH	MDPH
NS	83 (66%)	4 (80%)
MC	14 (11%)	1 (20%)
Other	28 (22%)	0 (0%)
Total	125	5

p=0.41

NS = nodular sclerosis

MC = mixed cellularity

Table 14: EBV genome positivity in MDPH and HSPH Hodgkin's Disease Participants

EBV	HSPH	MDPH
Positive	22 (18%)	1 (20%)
Negative	100 (82%)	4 (80%)
Total	122	5

OR=0.88, p=0.91

TABLE 15  
 1982 - 1999 Hodgkin's Disease Incidence, Methuen, Massachusetts

Cancer Type	Total			Male			Female					
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
1982-1990	17	13	130	76 -- 208	11	6.8	161	80 -- 288	6	6	96	35 -- ##
1990-1995	9	8.9	101	46 192	6	4.8	124	46 272	3	4	NC	NC
1995-1999	13	7.3	179	95 305	9	4	224*	103 427	4	3	NC	NC

Note: SIRs are calculated based on the exact number of expected cases  
 Expected numbers of cases presented here are rounded to the nearest tenth  
 Obs = Observed number of cases  
 Exp = Expected number of cases  
 SIR = Standardized Incidence Ratio  
 NC = Not calculated when observed < 5.  
 \* = Statistical significance

FIGURE 1  
Methuen - Hodgkin's Disease

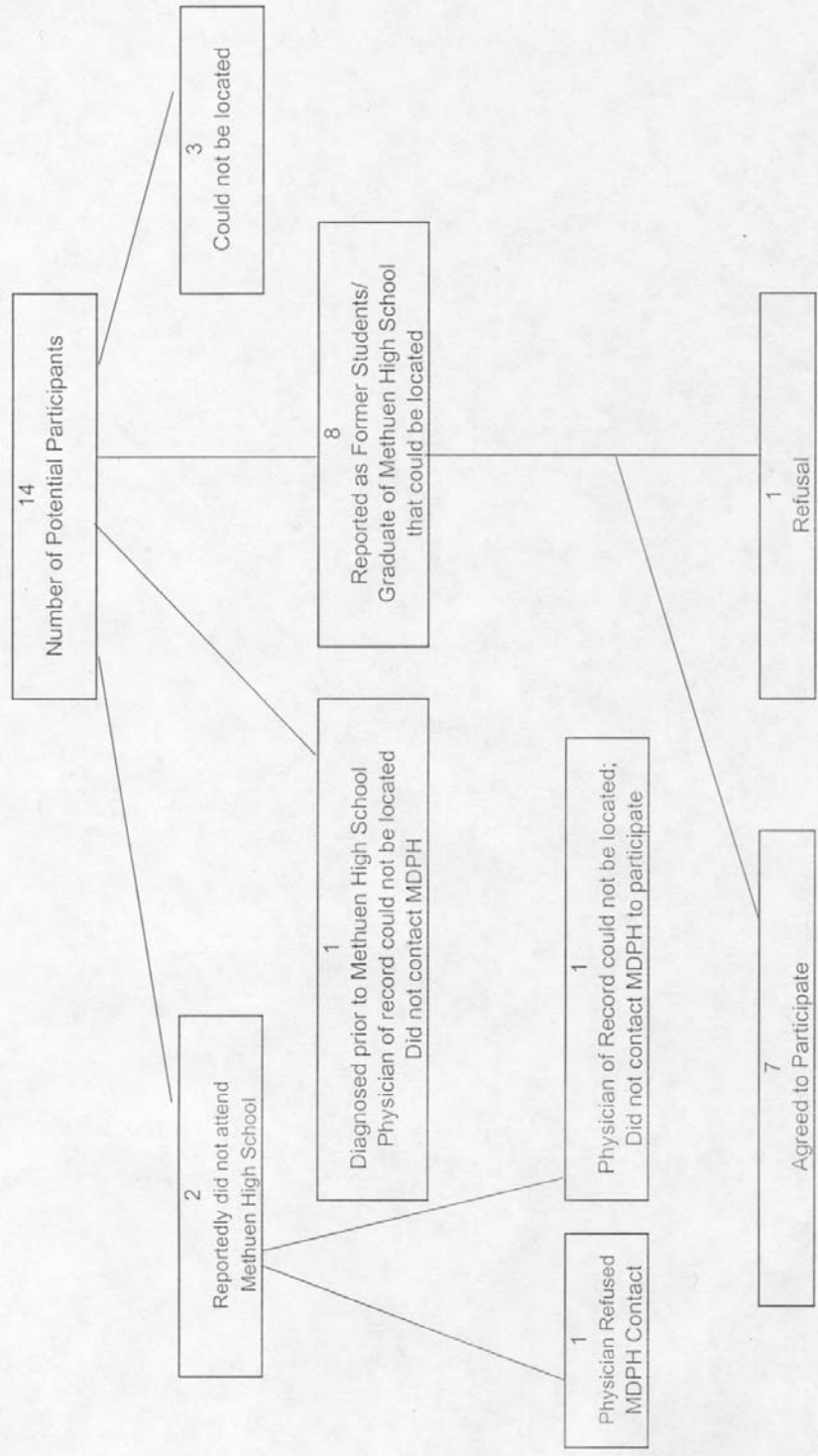
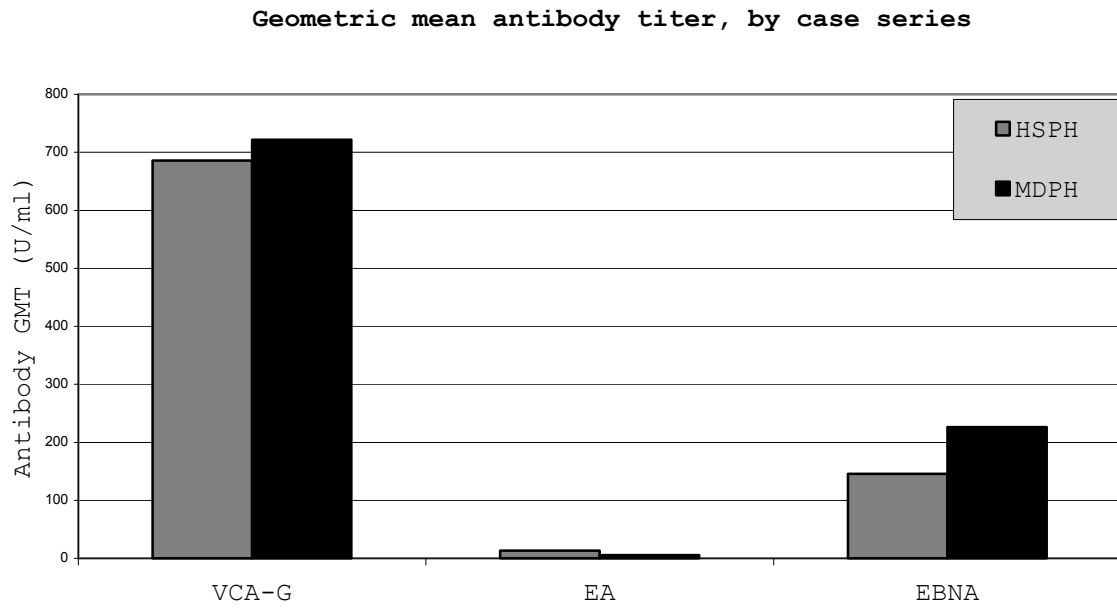


Figure 2





## Appendices