Case-control studies of Hodgkin’s disease have been performed to investigate 4 general areas. First, Hodgkin’s disease cases have been compared with control groups that bore some special environmental relationship to the cases. These were done to give some idea of different patterns of occurrence of the disease. Second, case-control studies have been conducted to test a specific hypothesis regarding a suspect etiological factor or event. Third, serological differences between cases and controls have been measured in order to incriminate a possible etiological agent. Fourth, several laboratories have looked at differences in HL-A frequency among cases and controls in order to identify a genetically determined group that may be unusually susceptible to developing the disease.

The types of studies referred to represent case-control studies in which the controls, whatever type they were, were selected specifically for one reason or another before the investigation began. This is in contrast to those studies dealing with clustering phenomenon or suggesting a case-contact-case spread of the disease in which the “controls” or various types or contacts are not specifically chosen but rather result from the conduct of the study.

We undertook a collaborative case-control study of Hodgkin’s disease in 2 geographic areas, using essentially the same methodology, in order to combine several aspects of previous case-control studies (6, 11). Specifically, we were interested in following up on the suggestion that tonsillectomy may be a risk factor in Hodgkin’s disease, to look for additional clues to disease etiology that may come from a historical questionnaire to see whether prior infectious mononucleosis or history of exposure to infectious mononucleosis might be a risk factor in Hodgkin’s disease, to assess serological differences between cases and controls with respect to EBV and other herpesviruses, and to evaluate differences in HL-A type between cases and controls. The study consisted of both historical and serological survey of prevalent cases of Hodgkin’s disease and matched controls.

Tonsillectomy

Vianna et al. (15) found that tonsillectomy increases the liability to the subsequent development of Hodgkin’s disease by a factor of 2.9 times. Their 109 patients were all under the age of 40 and their controls were not matched specifically for socioeconomic status. A subsequent report did not confirm this association among 53 patients in Finland (15). Johnson and Johnson (8) presented data which they interpreted as also not supporting the findings of Vianna et al. (15), although reanalysis of their data by 3 groups done independently (3, 12, 14) indicate a relative risk of 2.0 for Hodgkin’s disease patients which is consistent with the estimate of 2.9 by Vianna et al. (15), although it is not statistically significant at the 0.05 level (Table 1). We did not find that patients gave a prior history of tonsillectomy significantly more than matched controls (Table 2), siblings or spouses.

The reasons for these inconsistencies are not known. Although Vianna et al. (15) did not match their controls specifically by social class, there was no difference between their cases and controls by education or occupation, the 2 factors on which our social class measure is based (11). Also, if social class were the confounding variable, one would not expect an increased risk in the Johnson and Johnson series (8), since siblings are an excellent match for social class.

Infectious Mononucleosis

Miller and Beebe (10) recently reviewed the possible association between infectious mononucleosis and the subsequent development of Hodgkin’s disease. Neither their prospective nor retrospective study demonstrated a relationship between clinical infectious mononucleosis and cancer in adult males. Data from our retrospective study (11) revealed a relative risk of 1.4 for a prior history of infectious mononucleosis among Hodgkin’s disease cases, thus confirming their negative observations.

Prior Drug Use

An unexpected finding in our case-control study (11) was a significant difference in prior history of having taken Dexedrine (or amphetamine) prescribed mostly for weight reduction (Table 3). Hodgkin’s disease patients had a 6-fold increase in prior history of Dexedrine use when compared to

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1 Presented at the International Symposium on Human Tumors Associated with Herpesviruses, March 26 to 28, 1973, Bethesda, Md. Studies referred to in this discussion were supported under Contracts NIH 71-2423 from the Epidemiology Branch, National Cancer Institute; PH 43-68-1030 within the Special Virus Cancer Program of the National Cancer Institute, NIH, USPHS; and Research Career Development Award 1 KO4 CA 70116-01 (Dr. Newell) from the National Cancer Institute.

2 Presented by.

The abbreviations used are: EBV, Epstein-Barr virus; GMT, geometric mean antibody titer.
Guy R. Newell and Brian E. Henderson

Table 1
Distribution of 85 matched pairs according to patient’s and sibling’s tonsillectomy history (8, 12)
Relative risk = 15/7 = 2.1. p = 0.07.

<table>
<thead>
<tr>
<th>Sibling’s history</th>
<th>Patient’s history</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Negative</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 2
Distribution of 176 matched pairs of Hodgkin’s disease and controls by tonsillectomy history (11)
Relative risk = 1.2. x^2 = 0.06.

<table>
<thead>
<tr>
<th>Control’s history</th>
<th>Patient’s history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>39</td>
</tr>
<tr>
<td>Negative</td>
<td>44</td>
</tr>
</tbody>
</table>

matched nonrelated controls. The increase in risk for Dexedrine users was present for both males and females in both young and older adults and for nodular sclerosis and mixed cellularity subtypes. We could find no specific reference relating lymphomas or Hodgkin’s disease to amphetamine use with the exception of a report of Hodgkin’s disease in a married couple (1). Both patients were said to participate in the “hippie” and drug subcultures and freely took lysergic acid diethylamide, tyramines (a short-acting sympathomimetic amine structurally similar to amphetamines), and marijuana (1). There is one report of a case of acute myeloblastic leukemia occurring in a Benzedrine addict, and others have reported severe anemia, pancytopenia, and megaloblastic anemia following Benzedrine use (2).

Of special public health concern, should this finding be confirmed in future studies, is the potential for children treated with amphetamines for hyperkinesis (5) being at high risk for future development of Hodgkin’s disease. It is estimated (1971) that 150,000 to 300,000 children nationally are being treated with psychoactive drugs for hyperkinesis and it has been claimed that from 3 to 10% of children in America suffering from this disorder might benefit from drug treatment (4).

**EBV and Other Herpes Group Antibody**

Previous studies (7, 9) have reported significantly increased EBV antibody titers in Hodgkin’s disease. Levine et al. (9) found elevated EBV antibody titers in all 4 histological types of Hodgkin’s disease, although highest titers were found in the mixed cellularity and lymphocyte depletion types.

In our group of Hodgkin’s disease patients, antibody titers, to EBV were significantly elevated (GMT = 92.0) compared to matched clinic (GMT = 52.6), spouse (GMT = 53.5), or sibling (GMT = 32.2) controls (Table 4). The GMT’s of the lymphocyte predominant type were not significantly different from controls but were significantly lower than titers in cases of nodular sclerosis or mixed cellularity (Table 5).

Varicella antibody titers were significantly elevated in Hodgkin’s patients compared to matched and spouse controls, but not in sibling controls. There were no significant differences in antibody titers to herpes simplex type 1 and cytomegalovirus in Hodgkin’s patients compared to the different control groups. There was no significant variation in GMT to herpes simplex, varicella, and cytomegalovirus by histological type.

These results suggest that EBV is not important in the etiology of at least 1 form, lymphocyte predominant, of Hodgkin’s disease. If it is not related to this histological

Table 3
Distribution of 100 matched pairs of Hodgkin’s disease and controls by Dexedrine history (11)
Relative risk = 6.3. x^2 = 10. p = 0.01.

<table>
<thead>
<tr>
<th>Control’s history</th>
<th>Patient’s history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>6</td>
</tr>
<tr>
<td>Negative</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 4
EBV antibody titers in Hodgkin’s cases and matched clinic, spouse, and sibling controls

<table>
<thead>
<tr>
<th>Group</th>
<th>No. tested</th>
<th>Geometric mean titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s cases</td>
<td>142</td>
<td>92.0</td>
</tr>
<tr>
<td>Matched controls</td>
<td>142</td>
<td>52.6</td>
</tr>
<tr>
<td>Hodgkin’s cases</td>
<td>62</td>
<td>109.4</td>
</tr>
<tr>
<td>Spouse controls</td>
<td>62</td>
<td>53.5</td>
</tr>
<tr>
<td>Hodgkin’s cases</td>
<td>51</td>
<td>93.6</td>
</tr>
<tr>
<td>Sibling controls</td>
<td>51</td>
<td>32.2</td>
</tr>
</tbody>
</table>

Table 5
EBV antibody titers in Hodgkin’s patients by histology

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>No. tested</th>
<th>10^*</th>
<th>160</th>
<th>GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte predominance</td>
<td>23</td>
<td>4 (17%)</td>
<td>5 (22%)</td>
<td>39.6</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>98</td>
<td>6 (6%)</td>
<td>45 (46%)</td>
<td>96.1</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td>8</td>
<td>0 (63%)</td>
<td>5</td>
<td>95.1</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>44</td>
<td>0</td>
<td>26 (59%)</td>
<td>160.0</td>
</tr>
<tr>
<td>Matched controls</td>
<td>173</td>
<td>10 (6%)</td>
<td>35</td>
<td>52.6</td>
</tr>
</tbody>
</table>

* Reciprocal of dilution.
type, it seems unlikely that it would be etiologically related to the other histological types since it is difficult to consider the lymphocyte predominant type a separate disease entity from the other histological types. In addition, the finding of elevated antibody levels to varicella virus and the occurrence of chicken pox as a complication of Hodgkin's disease, suggests that patients with Hodgkin's disease may have an altered ability to control the proliferation of other herpes-viruses besides EBV.

HL-A Antigens

It is possible that in humans there may exist an association between the HL-A loci and genes controlling immune response and susceptibility to viruses, as in the mouse. Because of this, there is a need for a more sophisticated approach to further define the factors determining host susceptibility to Hodgkin's disease. As noted previously (3), HL-A 1 and 8 were detected about twice as frequently in our Hodgkin's cases compared to all 3 different control groups. HL-A 9 was consistently detected about one-half as frequently in Hodgkin's cases. Additional study of family members and close associates who do not acquire the disease might provide insight into the specific immunological alteration occurring in Hodgkin's patients.

References

Discussion of Case-Control Study of Hodgkin's Disease

Guy R. Newell and Brian E. Henderson

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