Analysis of HL-A Antigens in Patients with Hodgkin's Disease and Their Families

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Abstract
The HL-A phenotypes of 127 patients with Hodgkin's disease have been determined. A very significant association has been found between Hodgkin's disease and two HL-A antigens, HL-A11 (P < 0.009), and W5 (P < 0.0005). The families of 40 of these patients were genotyped for HL-A antigens. A normal mendelian segregation of the relevant antigen was found in all 12 families of HL-All positive patients and in 6 of 8 families of W5 positive patients. These findings suggest that certain Hodgkin's patients have a genetically determined susceptibility to their disease. It is postulated that this susceptibility could be due to linkage between HL-A genes and genes controlling immune responsiveness. Analysis of subgroups of Hodgkin's patients based on age, sex, and pathology suggests that these HL-A associations are most marked in certain subgroups.

Introduction
Previous work by Amiel (1) and Forbes and Morris (2) has shown that certain HL-A antigens, namely 4c and an included antigen W5, occur with a significantly higher frequency in patients with Hodgkin's disease than in a normal population. Although van Rood, van Leeuwen, Schippers, and Balner (3) initially did not find any association between HL-A and Hodgkin's disease, antisera of the 4c specificity were not used in their analysis. More recently van Rood and van Leeuwen (4) in a further study of 98 patients with Hodgkin's disease were able to show an increased frequency of W5 in these patients. Other workers have found an increased frequency of W5 or other antigens included in 4c (5-7, 24). But Bodmer (1) was not able to show this in 44 patients from the San Francisco area. Nevertheless, the evidence to date strongly supports the existence of an association between antigens of the 4c group of cross-reacting HL-A antigens and Hodgkin's disease. This apparent association between HL-A antigens and disease could be due to the production of the relevant antigen by the disease process. Alternatively, the presence of the antigen before the onset of the disease could reflect an increased susceptibility for the disease.

The most acceptable interpretation of the serological data for HL-A is that it comprises two segregant series of antigens, which behave as if they were determined by mutually exclusive alleles of two closely linked loci. These alleles segregate as autosomal dominants through families. Hence analysis of the segregation of the HL-A antigens in families of patients with Hodgkin's disease could exclude the possibility that antigens associated with the disease are acquired as a result of the disease process.

It has already been established that the associations between transplantation antigens of mice and susceptibility to oncogenic viruses appear to involve transplantation antigens that are known to be present before challenge with the oncogenic virus (8-11). This suggests that the presence of the appropriate antigen in mice is associated with an increased susceptibility for the disease.

More recently, further associations have been reported between the major histocompatibility systems of mice and guinea pigs, and immune responsiveness to a number of synthetic antigens (12-16). McDevitt and Benacerraf have discussed at length the genetic control of immune responsiveness in guinea pigs and mice, and suggested that the action of immune response genes may result in the recognition or selection of antigenic determinants against which specific antibody is synthesized (12). More recently, Martin, Ellman, Green, and Benacerraf (15) showed that a gene determining response to poly-L-lysine (PLL) in guinea pigs may in

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fact be identical with a gene determining a major histo-
compatibility antigen.

On the basis of these observations and the work re-
ported in this paper, it is proposed that the association
between HL-A antigens and Hodgkin's disease may
represent an association between HL-A antigens and a
defect in the genetic control of the immune response
of some patients with Hodgkin's disease. The results
of the analysis of families of Hodgkin's patients re-
ported here, showing that the antigens related to
Hodgkin's disease segregate normally within patients'
families, is consistent with the above proposal. It is also
relevant that patients with Hodgkin's disease do have a
defect in their immune responsiveness (17).

METHODS

Leukocyte typing. A microlymphocytotoxic technique
(18) was used to type patients, their families, and an un-
related population of 273 normal Caucasian people in Mel-
bourne. All typings were performed on peripheral blood
lymphocytes prepared as previously described (19). All
patients were typed on at least three occasions.

Antisera. The antisera used were obtained from NIH
Serum Bank, multiparous women, renal transplant patients,
the Sydney and Melbourne Blood Transfusion Services,
and Doctors J. Dausset, W. Bodmer, P. Engelfriet, and P.
Terasaki. Altogether between 60 and 125 antisera were
used to detect 7 HL-A antigens of the first locus, 10 HL-A
antigens of the second, and the 2 complex antigens, 4a
and 4b. As this study extended over 2 yr, the same anti-
sera were not used to define HL-A specificities through-
out the study. The antisera detecting the antigens of greatest
interest in this investigation are shown in Table I.

W5 has been defined primarily by the sera designated as
MBTS Collihole and MBTS Mournellis (Table I). Both
these sera define an antigen which is allelic to HL-A5 as
redefined at the Fourth International Histocompatibility
Workshop by antisera Engelfriet CLB7 (WKS 72) and
Dausset Dub. (WKS 13). Both W5 and HL-A5 are in-
cluded for the most part in 4c as defined by Payne-Bodmer-
Rafter (WKS 47). Both the sera Mournellis and Collihole

<table>
<thead>
<tr>
<th>Table I</th>
</tr>
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<tbody>
<tr>
<td><strong>Antisera Used to Detect Certain HL-A Antigens</strong></td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>HL-A11</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4c</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HL-A5</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>W5</td>
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<tr>
<td></td>
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<tr>
<td>HL-A7</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4a</td>
</tr>
<tr>
<td>4b</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

r, correlation coefficient; WKS, number of serum used in
Fourth International Histocompatibility Workshop (23);
MBTS, Melbourne Blood Transfusion Service; SBTS, Sydney
Blood Transfusion Service; NZ, Auckland Blood Transfusion
Service.

NIH serum bank numbers are given where appropriate.

contain a weak anti-HL-A5, but the serum Collihole rarely
produces a positive reaction with HL-A5. Thus for prac-
tical purpose Collihole is considered to detect W5 alone.

Two by Two Correlations between Antisera Defining W5 and Those Defining HL-A5 and 4c,
and between Antisera Defining HL-A11 and Those Defining HL-A1 and HL-A3

<table>
<thead>
<tr>
<th>Table II</th>
</tr>
</thead>
</table>
| **Two by Two Correlations between Antisera Defining W5 and Those Defining HL-A5 and 4c,**
and between Antisera Defining HL-A11 and Those Defining HL-A1 and HL-A3 |
| Serum | vs. Serum | ++ | +/− | −/+ | −− | X² |
| Collihole (W5) | Mournellis (W5) | 34 | 2 | 10 | 250 | 222.3 |
| Collihole (W5) | P. E. Rafter (4c) | 28 | 7 | 41 | 218 | 67.2 |
| Collihole (W5) | Da. Dub. (HL-A5) | 4 | 27 | 32 | 221 | −0.06 |
| Da. Dub. (HL-A5) | P. B. Rafter (4c) | 29 | 2 | 37 | 216 | 92.1 |
| Da. Dub. (HL-A5) | Eng. CLB7 (HL-A5) | 27 | 5 | 3 | 250 | 199.9 |
| Arlaskus (HL-A11) | Th-EA (HL-A11) | 6 | 1 | 2 | 61 | 34.6 |
| Arlaskus (HL-A11) | W. Anderson (LC20) | 37 | 1 | 84 | 170 | 53.7 |
| Arlaskus (HL-A11) | Da. Roy (HL-A3-WKS 12) | 1 | 8 | 10 | 54 | −0.73 |
| Arlaskus (HL-A11) | P. B. Gillespie (HL-A1-WKS 56) | 10 | 30 | 91 | 165 | −2.21 |

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positive cells but rarely with HL-A3 positive cells (Table II).

Patients. Two consecutive independent series, comprising 35 and 92 patients respectively, have been studied. All patients were assessed upon referral to the Cancer Institute, Melbourne, and wherever possible, were assigned a pathological grade and clinical stage. The distribution of patients into appropriate grades and modes is shown in Table III. The two modal groups are based on age at presentation (20), the first comprising patients aged 15-34 yr at presentation, and the second, those patients aged 50 yr or more. The pathological grading has been based on the report of the Nomenclature Committee (Lukes, Craver, Hall, Rappaport, and Ruben [21], and the work of Lukes and Butler [22]. In all cases the pathological diagnosis is that made at the Cancer Institute from review of biopsies performed before referral or a biopsy performed at the Institute. Only patients who had the diagnosis of Hodgkin's disease confirmed have been included.

Family studies. The families of 51 of the 127 patients were suitable for genotyping for HL-A. Of these, 40 have been successfully genotyped such that the haplotypes (antigen pairs on a single chromosome) were determined with a reasonable degree of certainty. 70 parents and 131 children were directly typed, many on several occasions. Haplotype frequencies were determined by direct counting of the haplotypes. 13 of the unknown 20 parental haplotypes could be deduced from the sibling typing data.

RESULTS

Antigen frequencies. The normal antigen frequencies have been calculated from a control population of 273 healthy Caucasians. They agree closely with the published normal values of antigen frequencies as determined at the Los Angeles Workshop, 1970 (23).

A number of significant associations are shown between HL-A antigens and Hodgkin's disease (Table IV). Hodgkin's disease is treated here as a homogeneous entity, including all pathological grades. The association of Hodgkin's disease with antigens of the 4c region (which includes both W5 and HL-A5) has been reported previously (1, 2). It is seen that antigen W5 does have a very significant association. Furthermore, there is an apparent association with the antigen HL-A11, which has not previously been reported.

Clinicopathological parameters. Table III and IV show the frequency of some of the antigens in various subgroups of these Hodgkin's patients.

Although these subgroups are relatively small, some features of interest are seen. In the nodular sclerosis group (Table III) it is seen that the relatively high frequency of HL-A7 is most marked in the female patients. This is also true of the females with mixed cellularity Hodgkin's disease. In the lymphocytic predominance group (Table III) W5 is seen to be relatively common in males.

Table IV shows the distribution of antigens for male and female patients. It is of interest here that antigens HL-A1 and A8, and W5 were found to be more common in males and HL-A11 and A7 more common in females. The differences with HL-A11 and A7 are statistically significant when males are compared with females. These differences may be related to the preponderance of females among the nodular sclerosis group, where both HL-A11 and HL-A7 were found to be relatively more common than in the group as a whole.

Haplotype studies. The frequency of haplotypes as calculated from the family studies are shown in Table V. Two of the haplotypes (HL-A1-8 and HL-A2-12) each accounts for 8 of the 79 haplotypes. These are both known to be common in normal Caucasians (23). The actual antigen haplotypes as determined for each family are shown in Table VI.

Antigen segregation. There were eight families studied where the patient was positive for antigen W5. In six of these, the antigen appeared to have segregated in a normal manner from a parent to patient. In one
family, the parents were not available for typing, and
in the last of these eight, W5 was present in the patient,
but absent from both parents. This latter patient should
be homozygous for the antigen HL-A5, which is known
to cross-react with W5. This family is number 37 in
Table VI, and is shown in detail in Table VII. In all 12
cases where a patient had the antigen HL-A11, this
antigen was found to have segregated in a normal
manner.

Family 39 (Tables VI and VIII) also shows an
apparent abnormality. The patient was positive for
HL-A12, whereas both parents were negative. These
findings were unequivocal. In addition, the patient was
negative for HL-A9 when he should have typed as posi-
tive. This family was typed on two separate occasions
and the patient on three occasions, and identical results
were obtained each time. Unfortunately, no other sibling
information can be obtained in this family, and al-
though specific questioning of parentage was not under-
taken, the results of a limited analysis of red cell anti-
gens were compatible with the stated parentage.

### DISCUSSION

The association between antigen W5 and Hodgkin's
disease is still highly significant after appropriate cor-
rection is made for multiple comparisons.

As a comparison is made for 17 antigens between the
Hodgkin's and normal populations, there is a 1 in 17
chance of one of these comparisons being significant at
the 5% level. Hence P values should be corrected by
multiplying by the number of comparisons made (17 in
this study). However, the potential error in the analysis
of such associations is best excluded by demonstrating
the same increased frequency of a particular antigen in
two consecutive, independent prospective series of pa-
ents. This has been done by us for antigens W5 and
HL-A11.

It is of interest that a previous report noted an asso-
ciation between Hodgkin's disease and the antigens
detected by the antiserum Lc20 (24). This antiserum de-
tects more than one antigen including HL-A1 and -A3,
as well as -A11 (23). It seems from our results that the
increased frequency of Lc20 is in fact due to an increase
in the HL-A11 component, as in this and other series

### TABLE IV

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Normal Caucasians (273)</th>
<th>Hodgkin's Males (76)</th>
<th>Hodgkin's Females (51)</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>HL-A1</td>
<td>31.9</td>
<td>40.8</td>
<td>23.5</td>
<td>33.9</td>
</tr>
<tr>
<td>HL-A2</td>
<td>50.6</td>
<td>52.7</td>
<td>43.2</td>
<td>48.8</td>
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<td>27.6</td>
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<td>9.2</td>
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<td>HL-A11</td>
<td>13.6</td>
<td>19.7</td>
<td>43.2</td>
<td>28.4§</td>
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<td>W28</td>
<td>4.4</td>
<td>2.7</td>
<td>4.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Antigens of neither locus</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>65.2</td>
<td></td>
<td>69.3</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>80.5</td>
<td></td>
<td>89.8</td>
<td></td>
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</tbody>
</table>

* Chi squared = 23.4, P < 0.0005 (corrected for 17 comparisons, see text).
† Chi squared = 10.0, P < 0.05 (corrected for 17 comparisons, see text).
‡ Chi squared = 12.2, P < 0.009 (corrected for 17 comparisons, see text).

W, numbers refer to specificities defined at the Fourth International Histocompatibility Workshop (23).
116 patients were tested for HL-A11.

### TABLE V

<table>
<thead>
<tr>
<th>HL-A antigens</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>W28</th>
<th>X</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>W5</td>
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<td>W15</td>
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<td>1</td>
<td>7</td>
</tr>
<tr>
<td>W10</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>W22</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Y</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>9</td>
</tr>
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<td>Total</td>
<td>18</td>
<td>24</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>5</td>
<td>79</td>
</tr>
</tbody>
</table>

X represents undetected first locus antigen.
Y represents undetected second locus antigen.

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**Table VI**

*Haplotypes in Families of 40 Hodgkin's Patients*

<table>
<thead>
<tr>
<th>Family No.</th>
<th>Number of children</th>
<th>Father</th>
<th>Mother</th>
<th>Patient</th>
<th>Other children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>A1.A12</td>
<td>X.Y</td>
<td>A10.A5</td>
<td>X.A7</td>
</tr>
<tr>
<td>29</td>
<td>2</td>
<td>A2.A12</td>
<td>X.A5</td>
<td>X.W5</td>
<td>A2.A7</td>
</tr>
<tr>
<td>33</td>
<td>6</td>
<td>A3.A7</td>
<td>X.A12</td>
<td>X.W5</td>
<td>A1.Y</td>
</tr>
</tbody>
</table>

**Legend:**

X = Undetected allele of first locus.
Y = Undetected allele of second locus.
Families 37 and 39 are shown in Tables VII and VIII.

13 parental haplotypes were deduced from sibling typings.

* Patient's husband and son were typed.

the frequency of HL-A1 and -A3 is not significantly different from the normal for the group as a whole.

The results of the family studies suggest that the relevant antigens were present before the disease developed. In six cases where a patient was found to be W5 positive, the antigen was found to also be present on a parent's lymphocytes. The one case where W5 was present on a patient's lymphocytes and absent from a parent's lymphocytes probably reflected cross reactivity between HL-A5 for which the patient was homozygous, and the antigen...
A = W28.A5; b = A2.W10; c = X.W15 (X = undetected allele at first locus); d = A3.A5.
The positive reactions for W5 in the patient (confirmed on three occasions) may be due to cross reactivity between A5 and W5 in the presence of homozygosity for A5.

W5. These two antigens are known to cross-react, and hence may be detected by both anti-HL-A5 and anti-W5 antisera. In all other cases, including all of those where a patient was HL-A11 positive, the antigens appeared to have segregated in a normal manner from parent to patient.

These findings are very important, for they suggest that certain Hodgkin's patients developed their disease because of a pre-existing genetically controlled predisposition. This predisposition would not be the basis of the disease in all Hodgkin's patients, however, as not all Hodgkin's patients are positive for W5 or HL-A11; and not all people with W5 or HL-A11 develop Hodgkin's disease. It is important in this context to note that Hodgkin's disease is a very heterogeneous entity in both its pathological and clinical picture.

If, then, as our results suggest, the presence of the antigen does reflect a predisposition to Hodgkin's disease, it is important to consider why this might be so. There are two possible explanations.

Firstly, the antigen might be directly involved in the development of the disease process. For example, the antigenic determinant of an oncogenic virus could cross-react with the HL-A antigen W5, such that the virus is not recognized as foreign and hence is able to produce disease unhampered by an immunological response by the host. There is no existing evidence that this could not occur. Again the antigen W5 might represent a favored receptor site for viral attachment. However, the fact that not all people with W5 develop Hodgkin's disease suggests that additional factors would also have to be important.

Secondly, the presence of the antigen W5 could be associated with a predisposition to Hodgkin's disease if the genetic control of the antigen was linked to other genetic factors which themselves predisposed to the development of the disease. Thus a patient could inherit both a predisposition to the disease, and also the gene(s) determining the expression of antigen W5. There is, in fact, important experimental evidence that is consistent with this latter suggestion.

It is now established that in guinea pigs and mice there is a linkage between certain genes controlling the immune response and genes controlling the production of transplantation antigens (12-16). It is also well established that susceptibility to carcinogenesis in mice is related to particular transplantation antigens (8-11). There appears to be a similar relationship in man between Hodgkin's disease and the transplantation antigens W5 and HL-A11. It is possible, then, that there could be further relationship in man, i.e., between some genes controlling immune responsiveness and genes controlling HL-A antigens. If this were so, the presence of W5 in Hodgkin's patients could reflect the presence of certain immune response genes. Thus a genetic predisposition for Hodgkin's disease could involve immune response genes and be reflected in the observed association between Hodgkin's disease and HL-A antigens.

This is particularly relevant to Hodgkin's disease, as it is patients with Hodgkin's disease who are known to have well-defined defects in immune responsiveness (17). These defects involve predominantly the thymus-dependent components of the immune system, and it has

### Table VII

**HL-A Phenotyping of Family 37**

<table>
<thead>
<tr>
<th>Person</th>
<th>A2</th>
<th>A3</th>
<th>W28</th>
<th>A5</th>
<th>W5</th>
<th>W15</th>
<th>W10</th>
<th>Genotype</th>
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<tbody>
<tr>
<td>Father</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<td>+</td>
<td>-</td>
<td>-</td>
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<td>+</td>
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<td>+</td>
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### Table VIII

**Family 39**

<table>
<thead>
<tr>
<th>A2</th>
<th>A3</th>
<th>A11</th>
<th>A9</th>
<th>A5</th>
<th>W5</th>
<th>A7</th>
<th>A12</th>
<th>ABO</th>
<th>Rh</th>
<th>MN</th>
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</tbody>
</table>

Patient has HL-A12. This is absent from all other family members. Red cell serology is consistent with patient having father shown here.
been suggested that the appropriate genes determining
the immune response of mice to certain synthetic anti-
gens may also involve this system (16). It is not estab-
lished, however, whether these known defects preceed or
follow the onset of the disease.

Burnett’s proposals for a system of immunosurveillance
(25) could readily incorporate these ideas. Thus the
transplantation antigens possessed by an individual would
not only be used by him as a reference marker to iden-
tify foreign antigens (e.g., tumor cell-associated anti-
gens due to somatic mutation or viral oncogenesis) but
also could reflect a profile of immune responsiveness.
This may be most relevant to those tumours afflicting
younger people rather than those that occur in older
age groups, where immunological defects may be more
widespread as a result of the ageing process (25–26).

The relationships of antigens W5 and HL-A11 to
various pathological grades and clinical parameters are
not as yet sufficiently clear. These studies must be ex-
tended. There does appear to be a difference in the fre-
quency of certain antigens between males and females
(Table IV). HL-A11 is particularly common in females.
This could well be related to the variations in Hodgkin’s
disease that occur with different sexes; for example, the
presence of HL-A11 may particularly predispose to nodu-
lar sclerosing Hodgkin’s disease in females. Furthe-
more, the pathological variations seen on sections of
Hodgkin’s tissue probably reflect the variability of host
response to the disease process. Hence, if HL-A antigens
were involved in immune responsiveness, it would be
expected that certain antigens would be associated with
particular pathological grades, just as we have found
with HL-A11 and females with nodular sclerosing
Hodgkin’s disease.

In conclusion, it can be said that there is an associ-
ation between Hodgkin’s disease and HL-A antigens, and
family studies have shown that these antigens segregate
normally. The implications of these results are that cer-
tain patients with Hodgkin’s disease developed their
disease because of a genetically determined predisposi-
tion. This predisposition could involve control of the
immune response, and possibly determine the nature of
the pathology produced.

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