Human Histocompatibility Antigens in Normal and Neoplastic Tissues

J. J. van Rood, A. van Leeuwen, A. Schippers, and H. Balner

Department of Immunohaematology, University Hospital, Leyden, The Netherlands

Summary

More than 20 different leukocyte or tissue antigens can presently be recognized; they belong to one complex system (HL-A) which is, from the genetic point of view, very similar to the H-2 system in the mouse. Another independent system consisting of two antigens has also been well defined, the Group Five system.

The methods of defining these antigens, their tissue distribution, and complex relationships are described. The present knowledge of their chromosomal location, as derived from the analysis of family studies, is also presented and the practical implications of the occurrence of identical “alleles” in random populations is discussed. Finally, speculations about the relevance of these antigens in oncology and a few hopeful avenues for future immunotherapy (based on the present knowledge of human transplantation antigens) are indicated.

The relevance of these antigens in malignancy is as yet unknown, but hopeful avenues for further research do exist.

Introduction

The study of human histocompatibility antigens has been very fruitful in recent years. A detailed review has been published elsewhere (33); here a brief summary of the most important aspects will introduce a discussion of the possible significance of tissue antigens in oncology.

Recognition of Histocompatibility Antigens

The histocompatibility antigens have been shown to be at least partially identical to the leukocyte or tissue antigens. The ABO antigens, which are also histocompatibility antigens, will not be discussed here (10).

Most of the leukocyte antigens have been found by means of the so-called “computer approach” (36), in which a large number of sera are tested against 100 or more leukocyte samples and the resulting data are analyzed with a computer to select sera that recognize identical or antithetical antigens. These sera are then investigated for monospecificity and tested in population and family studies. The important advantage of the “computer approach” is that it greatly facilitates the selection of two or more sera with antibodies that recognize the same antigen. The availability of two or more sera of identical specificity makes it possible to correct for typing errors, still the main pitfall in this field.

For the recognition of the first ten well-defined antigens, the agglutination test mainly has been used (25, 31, 35, 36). But more recently the cytotoxicity test has become more popular, particularly since the introduction of a reliable microtest by Terasaki (18, 20, 46, 47).

Most workers use antibodies formed during pregnancies, but antibodies developed after planned immunization by skin grafting and/or blood transfusions are also being used (4, 5, 20, 30, 34, 38, 47).

The first antigen recognized by our group with the computer approach was called 4a; the antithetical antigen was called 4b. Pursuing the computer approach, our group has since recognized and defined 12 different antigens (25, 35, 36, 41), but the total number of antigens that can be recognized at present is well over 20 (32). This is illustrated in Table 1, which summarizes the most important and significant findings of the Torino Workshop, where 16 teams compared the reaction pattern of about 600 antisera against a panel of almost 100 leukocyte samples. As is evident from this Table, many of the teams were able to recognize, with varying degrees of accuracy, the same antigens (32).

The 4a antigen appears to be quite complex. Dausset (15) suggested, on the basis of an analysis of 50 sera with the computer approach, that a number of subgroups of antigen 4a exist. This assumption has since been confirmed and further substantiated, notably by Ceppellini et al. (11), who showed that a serum with strong cytotoxic antibodies of clearcut anti-4a specificity could by absorption be split up into at least five different antibodies that recognized antigenic determinants most of which were included in 4a; i.e., they were rarely present when the main 4a antigen was absent. The possibility that these antigens recognize not variants or “parts” of the 4a antigen but closely linked antigens of different specificity has not been excluded, however. Although sera with anti-4b reactivity are readily found when sought with the ethylenediaminetetraacetic acid (EDTA) agglutination test, cytotoxic antibodies with similar specificity are rare. Of the two known examples, one was formed after isoimmunization of a chimpanzee which was typed as 4b negative and immunized with skin and leukocytes from a chimpanzee positive for 4b (4).

The 4a and 4b antigens can still be considered as alternatives, but since family studies have shown that one chromosome can carry the genetic information for both of them, they are thus not mutually exclusive.

Antigen 6a is apparently a weak one. Of the original three anti-6a sera, only one has remained strong enough for use, and no new reagents of this kind have been found. Anti-6b antibodies are easier to find with the EDTA agglutination test than with the cytotoxicity test; nevertheless, two cytotoxic antibodies with such specificity have probably been found. Antigens 6a and 6b are alternatives, but family data showed a
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Dauset</th>
<th>Payre</th>
<th>Terasaki</th>
<th>Coppielli</th>
<th>Bodmer</th>
<th>Engelfried</th>
<th>Kismayer</th>
<th>Laasari</th>
<th>Leeke</th>
<th>Waldoff</th>
<th>Zmiajewski</th>
<th>Ames</th>
<th>Batchelor</th>
<th>Baker</th>
<th>Aniel</th>
<th>Shulman</th>
<th>Frequency of antigen (%)</th>
</tr>
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<tbody>
<tr>
<td>4a</td>
<td>4a</td>
<td>4a1</td>
<td>4a</td>
<td>4a</td>
<td>4a</td>
<td>4a*</td>
<td>4a</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>D5</td>
<td></td>
<td></td>
<td></td>
<td>T12</td>
<td></td>
<td>69</td>
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<td>11</td>
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<td></td>
<td>44</td>
<td>17</td>
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<tr>
<td>5*</td>
<td>&lt;</td>
<td>5</td>
<td>7</td>
<td></td>
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<td></td>
<td>14</td>
<td>64</td>
<td></td>
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</tr>
<tr>
<td>4b</td>
<td>6c</td>
<td>6c</td>
<td>4b</td>
<td>E1</td>
<td>4b</td>
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<td>26</td>
<td>90</td>
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<tr>
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<tr>
<td>7a</td>
<td>4d</td>
<td>6</td>
<td>T19</td>
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<td></td>
<td></td>
<td></td>
<td>C65</td>
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<td>2</td>
<td>37</td>
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<td>7c</td>
<td>10</td>
<td>5*</td>
<td>3</td>
<td>4b</td>
<td>6b</td>
<td>&lt;</td>
<td>C66</td>
<td>&lt;</td>
<td>38</td>
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<td>38</td>
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<td>7d</td>
<td>8</td>
<td></td>
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<td>1</td>
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<td>41</td>
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<td>23</td>
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<tr>
<td>LA1</td>
<td>11</td>
<td>LA1</td>
<td>1</td>
<td>8</td>
<td>LA1</td>
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<td>34</td>
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</tr>
<tr>
<td>8a</td>
<td>2</td>
<td>LA2</td>
<td>2</td>
<td>14</td>
<td>LA2</td>
<td>8a</td>
<td>LA2</td>
<td>42</td>
<td>5</td>
<td>B1</td>
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<td>61</td>
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<tr>
<td>LA5</td>
<td>12</td>
<td>LA3</td>
<td>10</td>
<td>LA3</td>
<td>LA3</td>
<td>LA3</td>
<td>HILL</td>
<td>25</td>
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<td></td>
<td></td>
<td>28</td>
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<tr>
<td>5a</td>
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<td></td>
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<td></td>
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<td>34</td>
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<tr>
<td>5b</td>
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<td></td>
<td></td>
<td>97</td>
<td></td>
<td></td>
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</tbody>
</table>

Most of these data were collected during the Torino Workshop 1967 (33). We did not use the anti-LA1 and anti-LA5 sera there. At the top of the Table the name of the principal investigator is given. At the bottom of the Table is indicated which technic(s) was (were) used by the investigator. If an antigen is in italics it implies that the antigen and the other italicized antigens reacted identically with all 96 leukocyte samples of the panel. Asterisks indicate subgroups.
Histocompatibility Antigens

Table 2

<table>
<thead>
<tr>
<th>Matings</th>
<th>No.</th>
<th>(6a+b)</th>
<th>(6a+b+)</th>
<th>(6a-b+)</th>
</tr>
</thead>
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<tr>
<td>(6a+b \times 6a+b)</td>
<td>27</td>
<td>100 (100)</td>
<td>71 (64)</td>
<td>1 (11.75)</td>
</tr>
<tr>
<td>(6a+b \times 6a+b+)</td>
<td>29</td>
<td>57 (64)</td>
<td>40 (23.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(6a+b+ \times 6a+b)</td>
<td>15</td>
<td>6 (11.75)</td>
<td>15 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(6a+b+ \times 6a+b+)</td>
<td>7</td>
<td>15 (15)</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(6a-b+ \times 6a+b)</td>
<td>0</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(6a-b+ \times 6a+b+)</td>
<td>4</td>
<td>163 (175.75)</td>
<td>130 (106.5)</td>
<td>5 (15.75)</td>
</tr>
</tbody>
</table>

| X^2 = 25.76 | P < 10^{-4} |

Family studies on the subgroup Six of the HL-A system. There exists a significant excess of heterozygotes in the offspring. The expected frequencies are given in parentheses. For further discussion see text. (This table is taken from Reference 40, courtesy of the publisher.)

significant excess of heterozygotes (Table 2). We have no definite explanation of this observation. It seems conceivable that a selective factor is at play, such as that described for certain isoantigens of the rat (28). Similar observations have been made by Ceppellini et al. (11) for his antigen TO-7 (= 7d). Obviously, such a finding would be of considerable biological interest because it could provide an explanation for the maintenance of the polymorphism of these antigens (29). It is, however, also possible that the 6a antigen is sometimes superimposed upon it. This would be similar to the situation believed by some investigators to exist for the MN system (42).

The serological definition of the 7a antigen has never been quite satisfactory. The antibodies were probably not monospecific and have become weaker. It is uncertain whether 7a is identical to T19 of Kusmeyer-Nielsen and PiGrLyC of Shulman. Possibly these three are different antigens, though they certainly show a highly significant positive association. Antigen 7b is again a weak antigen; no new anti-7b antisera have been found. Antigens 7a and 7b show a significant positive association in population studies. So far 7b, 7c, and 7d appear to be mutually exclusive on the chromosome. 7c and 7d are recognized by many investigators. Antigen 7c is highly significant and has become weaker. It is uncertain whether 7a and 7b are true alternatives. 7a is a weak antigen; no new anti-7a antisera have been found. Antigens 7a and 7b are true alternatives. 7a is a weak antigen; no new anti-7a antisera have been found.

Antigens LA1, LA2, and LA3 were recognized and described by Payne and Bodmer (8, 31), who also used the computer approach. These antigens are true alternatives. The complexity of the interrelationships between them is shown by the fact that a fourth antigen alternative to LA1, LA2, and LA3 recognized by Bodmer and called LA4, appears to be a subgroup of 4a (Table 1). LA2 is identical or closely related to Mac of Dausset (13), PiGrLyC1 of Shulman (44), and our 8a (41).

Antigens 5a and 5b are true alternatives. 5a is a weak antigen (25, 41). Three anti-5a sera have been found in Leyden since 1962; a fourth is possibly known in Capetown by Botha and Voogs. Anti-5b antibodies are quite frequent, but they can as yet only be recognized by the EDTA agglutination test (24). Torino 1 (Buffo) and NA1 are the same antigens. This antigen is present only on neutrophils, as are NB1 (not shown in Table 1) and probably 9a (23).

Genetics

On the basis of the results obtained from family studies, we have suggested that many of these antigens might belong to one leukocyte group system similar to the H-2 system in the mouse (41). A similar hypothesis was formulated by Dausset et al. (15) for the distribution of the antigens on the basis of association data in population studies.

The relative values and shortcomings of these two approaches have been extensively discussed by Ceppellini et al. (11). Although association data can give useful information, family data are far more informative and reliable. Many investigators have collected and published additional data of family studies (6, 7, 11, 14, 40, 48). The result of these studies tend to indicate that antigens 4a (and subgroups), 4b, 6b, 7a, 7c, 7d, and LA1, LA2, and LA3 all belong to one complex leukocyte group system called HL-A, previously also called Group Four, LA, Hu-1, Du-1, etc. The information for 6a and 7b is, as yet, incomplete, but from population studies it appears likely that they belong to the same system. Recombinants between HL-A and 9a have been found, but some evidence of linkage is accumulating; Group Five segregates independently from the two previous groups. Chart 1 summarizes the situation schematically. The HL-A system resembles in many ways the Rhesus or Gm system: i.e., it can be visualized as an extended chromosomal segment with a number of different mutual sides which we call 4, 6, 7, and S (= LA), between which crossing-over might occur, although at the moment no certain cases have been observed. However, nothing is known as yet about the actual structure of the HL-A locus, and subloci are indicated here in their numerical order only. What is known so far of the immunogenetics of the HL-A system is thus very reminiscent of the H-2 system of the mouse.

The fact that in man, as in the lower animals, most of the stronger transplantation antigens belong to one complex system is for a number of reasons both theoretically and practically important. With the help of family studies, the chromosomes or alleles (as combinations of the various alleles of 4, 6, 7, etc.) of the parents can be deduced from the patterns shown by their children. When 40 families were analyzed in this fashion, it was found that some of the alleles occurred, as expected, more frequently than others. The high frequency with which some of them occurred was, however, unexpected. Table 3 shows the most frequently encountered alleles.

The frequent occurrence of these alleles has a number of interesting implications. This is elaborated in Table 4, where it is shown that in 26 of the 40 families all four of the HL-A alleles of the parents were different. We have designated them...
80 parents studied. When α7a or α8a are lacking in the genotype, these alleles were deducted from the analysis of 40 families. The percentage indicates how often an allele was encountered in the population studied. This table is taken from Reference 40, courtesy of the publisher.

Chart 1. Schematic presentation of the localization of the genetic information of the leukocyte antigens on the chromosome. The information for the antigens of the HL-A system is located in a small section of the chromosome and is unequivocally supported by family studies. Subloci (4, 6, 7, and 8) might exist in the HL-A locus. In this schematic presentation, the subloci are arranged in their numerical order; nothing is known as yet about their actual arrangement. The locus for the Group Nine system might be on the same chromosome as the HL-A locus, but if so is certainly separated from it. The locus of the Group Five system is independent of the loci of HL-A and Group Nine systems. (This chart is taken from Ref. 40, courtesy of the publisher.)

The 10 most frequently encountered alleles or chromosomes. These alleles were deduced from the analysis of 40 families. The percentage indicates how often an allele was encountered in the 80 parents studied. When a7a or a8a are lacking in the genotype, it implies that the serologic reaction with anti-a7a or anti-a8a had been negative. α7c is so far a silent allele of a7b, a7d, and a7e.

<table>
<thead>
<tr>
<th>Mating type</th>
<th>Donor-recipient combination</th>
<th>% identical</th>
</tr>
</thead>
<tbody>
<tr>
<td>αb x cd</td>
<td>Parent-child</td>
<td>0</td>
</tr>
<tr>
<td>ac ad bc bd</td>
<td>Sib-sib</td>
<td>25</td>
</tr>
<tr>
<td>Mating type B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>αb x αd</td>
<td>Parent-child</td>
<td>25</td>
</tr>
<tr>
<td>aa ab ad bd</td>
<td>Sib-sib</td>
<td>25</td>
</tr>
<tr>
<td>Mating type C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aa x αc</td>
<td>Parent-child</td>
<td>0</td>
</tr>
<tr>
<td>ab ac ab ac</td>
<td>Sib-sib</td>
<td>50</td>
</tr>
</tbody>
</table>

Relation between the genotypes of the parents and the occurrence of identical leukocyte groups in a family. Of these 40 families analyzed, 26 belonged to mating type A, 10 to mating type B, and 4 to mating type C. For each mating type it has been indicated which percentage of the donor-recipient combinations will be identical when either a parent or a sib is the donor. It is evident that this percentage varies considerably in the different mating types. (This table is taken from Reference 40, courtesy of the publisher.)

Distribution in Cells and Tissues

That the leukocyte or tissue antigens are present on platelets has been shown by direct platelet agglutination (13), leukocyte agglutination inhibition (13, 34), mixed cell agglutination (12), and complement fixation (44), and can be inferred from the shortening of platelet survival time in the presence of leukocyte antibodies (9). Other cell lines and tissues have been far less adequately studied. For instance, the distribution of leukocyte antigens on granulocytes and lymphocytes has only been studied for the antigens PiGrLyH and PiGrLyC with complement fixation (44) and for the antigen 5b with agglutination inhibition (22). They have been demonstrated to be present on both. Very little is known about the differences in the amount of antigen present on either granulocytes or lymphocytes.

The red cell agglutination methods used in routine blood banking have failed to demonstrate the presence on the red cells of the leukocyte antigens discussed here. Nor has it been possible to absorb leukocyte agglutinins with leukocyte-free red-cell suspensions. However, by using a highly sensitive mechanical device, Rosenfield et al. (43) demonstrated the presence of hemagglutinins in almost all sera containing leukocyte antibodies. It was furthermore shown that some of these hemagglutinin-like substances are capable of absorbing leukocyte agglutinins.

Transplantation not only sib-sib but also parent-child donor recipient pairs which are identical for the HL-A system appear to do better than donor recipient pairs which are not identical (37). This observation might also be relevant for oncologic studies concerning the occurrence of malignancy in different generations of one family.

It is important to realize that the parents shown in mating type B are unrelated individuals and that the fact that identical parent-child combinations occur implies that HL-A identical unrelated individuals must exist as well; they have indeed been found. This point might be relevant for epidemiologic studies.

Distribution in Cells and Tissues

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The distribution of these antigens in organs has been studied for 4a, 4b, 6a, 6b, 7c, 5a, and 5b. A summary of the data obtained by leukocyte agglutination inhibition is given in Table 5 (J. F. Feddes, F. J. Cleon, and J. J. van Rood, unpublished observations). Only the presence of 4a, 4b, and 5b antigens has been studied for organs not shown in Table 5: they were found to be present in each instance.

The fact that anti-HL-A and anti-Five antibodies can be absorbed by platelets and various tissues does not in itself prove that these platelets and tissues carry the complete HL-A and group Five antigens. It could be that they only carry the hapten. Very little systematic work has been performed in man, except for the platelet studies. Bosch et al. (9) have shown that pure platelet suspensions rarely if ever induce circulating antibodies, while Dausset et al. (17) showed that platelets are hardly able to induce homograft sensitivity. Clearly, a good deal of work still remains to be done in this area.

As already mentioned, the 9a antigen is in all probability present on granulocytes only. It might thus fall in the same category as NA-1 (Buffo-To-1) and NB-1, which have been extensively studied by Lalezari (23). With this cell-line specificity, they can hardly be expected to be transplantation antigens.

**Relevance of Leukocyte Antigens in Transplantation**

Skin-grafting experiments have shown that at least five of the antigens of the HL-A system are transplantation antigens: 4a, 4b, 7c, 7d, and Mac(La2, 8a), (16, 41). Furthermore skin grafts exchanged between sibs survive significantly longer than nonmatched controls if donor and recipient type identical for HL-A antigens (1, 39). The relevance of the HL-A antigens in renal transplantation has already been mentioned (37, 46). A detailed account with a more complete list of references of the experiments and observations which showed that the HL-A antigens are transplantation antigens has been given elsewhere (33). In short it can be stated that there is reason to believe that the HL-A system is also from the biologic point of view the human counterpart of the H-2 system of the mouse.

**Relevance of Leukocyte Antigens in Oncology**

Very little is known as yet about the relevance of these antigens for malignancies, but four lines of research can already be distinguished:

**Comparison of the Frequencies of the HL-A and Group Five Alleles in Patients with a Malignancy Compared to Normal Individuals.** In a series of 50 patients suffering from leukemia and Hodgkin’s disease, we were unable to find significant differences in the distribution of the HL-A and group Five alleles as compared to those of the healthy population. Kourilsky and Dausset (21) studied the frequencies of HL-A antigens in more than 100 leukemic patients in remission and did not find a significantly different distribution either. Before a final conclusion can be reached, many more data must be available.

**Chorionepithelioma.** While studying one case of chorionepithelioma we were impressed by the presence of a strong similarity among the HL-A antigens of the patient and the husband (Table 6). The examination of additional cases showed that this similarity was not always present. In other words, some chorionepithelioma patients had at least one allele in common with their husbands, which implies that one out of four children in each case can be identical with the mother (Table 3). In other chorionepithelioma cases, patient and husband had no allele in common, which means that all the children will have an antigenic make-up different from that of the patient. The implications, if any, of these findings are unknown. One can speculate, of course, and wonder whether the prognosis in the first type of husband-wife combination would be bad and in the second one good. Studies are in progress to investigate this question further.

Considerations of this kind obviously also have some bearing on the question of whether immunotherapy is possible in chorionepithelioma cases. To immunize the patient herself might entail the danger of enhancement. We have therefore started the following immunotherapy: in cases in which every other form of treatment had failed, we immunized volunteers with skin of the patient’s husband and transfused the lymphocytes from the immunized volunteer to the patient.
used volunteers with HL-A groups identical to those of the patients. It is too early to comment on the effectiveness of this therapy.

Bone Marrow Grafting as Therapy in Leukemia. Efforts, notably those of Mathe et al. (26) to treat leukemia patients with total body irradiation followed by an infusion of normal allogeneic bone marrow have been disappointing since, with one exception, the patients succumbed to the extremely severe graft-versus-host disease typical for man and other primates. Preliminary findings made by Balner et al. (2) in Rhesus monkeys and Epstein et al. (19) in dogs suggest that the graft-versus-host disease will be significantly less severe if donor and recipient are identical for what might be called the equivalent of the HL-A system in these animals. This might reopen considerations regarding the use of bone-marrow grafting after total body irradiation for the treatment of leukemia. Even if donor and recipient are identical for the HL-A system, they may not be identical for the antigens of the group Five system and other as yet undefined tissue antigen systems. One could wonder whether this could be a final argument against the use of bone marrow grafts in the treatment of leukemia. However, a weak degree of incompatibility is desirable, because then the grafted cells might be able to kill the 1% of viable malignant cells remaining after total body X-irradiation. It is hoped that such a mitigated secondary disease can then be managed with the use of immunosuppressive agents.

The Use of Chimpanzees in the Study of Human Malignancies. As illustrated in Table 7, the chimpanzee carries the same or similar antigens as man does (4). Similar data have been reported by Metzgar and Zmijewski (27) and by Shulman (45). It is still unknown, however, whether the chimpanzee carries the same alleles as man. Probably due to this similarity of the tissue antigens, Balner et al. (3) were able to show that anti-human lymphocyte serum is able to prolong allogeneic skin grafts in chimpanzees quite significantly. This, incidentally, makes it possible to test antihuman lymphocyte serum for its biologic activity without having to resort to the obviously highly undesirable use of human volunteers. That the HL-A antigens of the chimpanzee are really identical or very similar to the human ones is borne out by the finding that chimpanzees can easily form anti-HL-A antibodies (4). This experimental fact makes it possible that antibodies against tumor-specific antigens might be produced by a tissue-compatible chimpanzee immunized against a patient’s tumor. From the same line of thought it follows that it would be interesting to investigate whether it is possible to transplant human tumors in chimpanzees to study the tumor’s characteristics, evaluate certain therapies, and possibly activate viruses that might be involved etiologically.

These, then, are four topics which appear to be relevant in the field of oncology. It might well be that the most important aspect lies elsewhere. The HL-A system is of unequalled genetic complexity, and the polymorphism forming the basis of this complexity must be maintained through some selective mechanism. The possibility should be considered that the same selective mechanism plays a role either in the control of somatic mutation, the defense against oncogenic viruses, or both.
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J. J. van Rood, A. van Leeuwen, A. Schippers, et al.


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