Review

HL-A Antigens: Association with Disease

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Recent advances have given rise to a relatively new field of medicine—transplantation immunology. Thousands of kidney as well as other organ transplants have been performed so far. The desire for a long-lasting graft enormously stimulated studies of so-called transplantation or histocompatibility antigens. These antigens, which for many years have been known to exist in both man and animals, have been studied extensively during the last decade. There is no doubt that one key to increasing graft survival is matching the donor and recipient with respect to histocompatibility antigens. The two must share as many antigens as possible. Consequently, there are now many "tissue typing" laboratories throughout the world.

Extensive work has been done not only on putative recipients and available donors of a particular organ but also on normal people as well as patients with a variety of diseases. An unexpected observation has emerged from these data: patients with some diseases show a distribution of the transplantation antigens which is different from normal. The number of reports showing such a relationship is growing very fast. Several reviews covering the subject have been published (McDevitt and Bodmer 1972; Dausset 1972a; Feingold 1971), and meetings on this topic have been held (McDevitt and Landy 1973 and Amos *et al.* 1973). Yet, in a recent review, Dausset, a pioneer in the field of human histocompatibility antigens, wrote, "There is a lack of convincing evidence for a correlation between the *HL-A* system and susceptibility to disease in man" (1972). The purpose of this review is to re-examine in a critical fashion the problem of HL-A antigens and susceptibility to disease in view of the latest published reports. Experimental animal data will not be detailed since they were reviewed recently (Benacerraf and McDevitt 1972; Bodmer 1972, and Snell 1968).

Genetics of the HL-A System. Histocompatibility antigens are present on all nucleated cells of a given organism. In both mouse and man the major histocompatibility antigens responsible for the strongest antigenic barrier to graft acceptance

are controlled by a single large chromosome region. This region is called the *H-2* system in the mouse and the *HL-A* system in man. Genetically, a system is defined by two or more linked loci, showing less than 1% recombination and linkage disequilibrium, i.e., alleles of the two loci do not combine randomly (Kissmeyer-Neilsen *et al.* 1972). The *H-2* and *HL-A* systems are considered homologous. It was suggested that *HL-A* is linked to the *PGM₃* locus determining the electrophoretic mobility of a phosphoglucomutase (Lamm *et al.* 1971) and possibly to the loci for the blood group P (Fellous *et al.* 1971).

HL-A is not sex-linked and therefore resides on one of the 22 autosomal chromosomes. The *HL-A* system is represented by two loci, referred to as *LA* (first) and *FOUR* (second), which are probably analogous to the *D* and *K* regions, respectively, of the *H-2* system.* Pedigree data have shown that *LA* and *FOUR* loci are closely linked. Each of these two loci has a distinct set of alleles that seem to be codominant. Each allele is expressed in a different HL-A antigen on the surface of the cells.

Haplotypes are pairs of alleles (or a "blank" corresponding to unrecognized alleles), one from *LA* and one from *FOUR* locus on a single chromosome. In general, the pairs will be inherited together by the offspring. Since chromosomes exist in pairs, the full expression of both chromosomes means that four HL-A antigens are detected ("full house") except in rare instances of homozygosity for an HL-A antigen or in the presence of a "blank."

Two or more alleles at a single locus occurring with an appreciable frequency in one population represent genetic polymorphism. So far at least 13 alleles are known in the *LA* and 17 in the *FOUR* loci, i.e., there are at least 30 corresponding HL-A antigens. Therefore, histocompatibility antigens give rise to an extreme degree of genetic polymorphism, suggesting that the *HL-A* system could be important in other biologic phenomena besides organ transplantation. For example, histocompatibility antigens may act as self-markers in a system of immune surveillance or, according to Jerne (1971), may determine and direct all immunological events within the organism.

Sampling and Statistical Pitfalls. Association of HL-A antigens with disease means an increased or decreased frequency of a specific antigen in a group of patients with a particular disease, compared to a group of normal people. As early as 1967 an association between HL-A antigens and disease was reported (Amiel 1967). The period of time since then can be divided into two parts. In the first part, up until 1972, the studies were most often retrospective and the association was weak and generally not significant due to pitfalls in statistical analyses. Only a small number of the presently known HL-A antigens was typed. This period was characterized by contradictory results, which forced Feingold to state in 1971, "that almost all the reported claims of associations between HL-A antigens and disease were fallacious" (Feingold 1971). Only during the second period, represented by the last few years, has the statistical association between HL-A antigens and several diseases been established unequivocally.

The pitfalls that can be found in associating a disease with a particular HL-A antigen may be classified into three groups: sampling errors, errors due to the technique of typing, and errors in the statistical analysis of results.

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*There is evidence suggesting the existence of a third *HL-A* locus (*SD* 3), probably more closely linked to the second (*SD* 2) than to the first (*SD*) *HL-A* locus (Solheim and Thorsby 1973).

Sampling Errors. Wide variations in the frequencies of particular HL-A antigens in various races are known (Albert *et al.* 1970, and Kissmeyer-Nielsen *et al.* 1971a). For example, HL-A 1, 3, 8 and W 14 are lacking in Japanese. Japanese and American populations are known to differ greatly in the occurrence of many diseases, such as carcinoma of the prostate or stomach. Geographic isolation may alter the distribution of HL-A antigens much as it does blood groups. Genetic disequilibrium could also explain the variation in a given finding from one geographical area to another. Spurious correlations between HL-A antigens and racially or culturally skewed diseases could be obtained easily if proper attention is not paid to these factors. In the case of lupus erythematosus, a difference between Negroes and Caucasians with respect to the frequency of HL-A antigens was reported. Antigen W 5 has an increased frequency in Negroes, while antigen W 15 is increased in Caucasians with the disease (Grumet *et al.* 1971 and Bitter *et al.* 1972). Caucasians with psoriasis or pemphigus have been found to differ in their association with a particular HL-A antigen according to their ethnic stratification (White *et al.* 1972b, Krain *et al.* 1973c). Patients with Hodgkin's disease from Norway had a decreased incidence of HL-A 11, those from Switzerland had a decreased incidence of W 10 while patients from the United States had a decreased incidence of HL-A 3 (Lawler 1973). Many diseases thus far studied are heterogeneous with respect to their histological and clinical attributes and in terms of the age of onset. The histological pattern of the disease has been found to play an important role in relating certain illnesses, such as Hodgkin's disease, to particular antigens (Falk and Osoba 1971). In this disease HL-A 7 was found particularly increased in females with the nodular sclerosing type (Forbes and Morris 1972). An association with HL-A 8 was found only in cases of dermatitis herpetiformis with intestinal involvement (Gebhard *et al.* 1973). In patients with retinoblastoma an increased frequency of antigen W5 was found in hereditary cases only (Bertrams *et al.* 1973a). The frequency of HL-A 17 was increased only in patients with psoriasis vulgaris and not in patients with pustular psoriasis (Svejgaard *et al.* 1973b). Disease heterogeneity, however, probably tends to dilute associations rather than give spurious ones. It might be suggested, therefore, that there is a better association of HL-A antigens with well defined subcategories of disease.

The age of the patient group has to be carefully matched with the control group. The age of onset appeared to be important in correlating diseases with certain HL-A antigens (Falk and Osoba 1971, and Burch 1971). For example, the incidence of HL-A 17 is clearly increased only in patients with psoriasis whose disease began early in life (Krain *et al.* 1973a), and HL-A 8 is increased in females with myasthenia gravis having an early age of onset while HL-A 3 is increased only in males with a late age of onset (Fritze *et al.* 1974). The influence of age, and even sex, with respect to disease association with HL-A antigens has been shown in the case of Hodgkin's disease (Falk and Osoba 1971, Forbes and Morris 1972, and Forbes and Morris 1970). However an increased frequency of HL-A 8 and HL-A 1 was found in both adults and children with celiac disease, irrespective of age (McNeish *et al.* 1973). It is noteworthy that the HL-A system shows no sex-related distribution in the normal population.

Typing Errors. At present, HL-A typing is carried out by cytotoxicity tests: i.e., the subject's cells, usually blood lymphocytes, are treated with human sera (alloantisera) that contain defined antibodies to different HL-A antigens (lymphocytotoxic alloantibodies) and with complement. A positive reaction results in loss of

restricted membrane permeability, e.g., injury or death of the cells. To assess different antigens, many typing antisera must be available. These usually are obtained from multiparous women or from multitransfused individuals. However, in the latter case, the antisera could be oligo- or multi-specific, e.g., contain antibody to one or more HL-A antigens. There are also cross-reacting antibodies, such as antibody to HL-A 3, which cross-reacts with HL-A 11, or antibody to HL-A 7, which cross-reacts with HL-A 27. Earlier, the number of known HL-A antigens was relatively small, but with the discovery of new antisera their number has been increasing rapidly. Some of the original so-called broad antigens have since been split into two or more narrow components. For example, the antigen 4c is now known to consist of HL-A 5, W 5, and W 18, with W 15 cross-reacting with them. Consequently, changes have resulted in the nomenclature of some HL-A antigens, which complicates the comparison between new and old reports. Periodic international workshops, intended primarily to compare different antisera, have resulted in a proposed WHO nomenclature for factors of the *HL-A* system.

Unlike most blood group antigens, the HL-A antigens are not stable. There is a constant and rather rapid shedding of HL-A antigens from lymphocytes, accompanied by the production of new antigenic material. The rate of turnover may be changed in some diseases, thus introducing another error in HL-A typing (Miyajima *et al.* 1972; Ceppellini 1971). It was claimed that two patients with leukemia had different HL-A antigens at different times (Pegrum *et al.* 1971). There have also been observations of cross-reaction between human transplantation antigens and antigens of different animals (Albert *et al.* 1969), or even bacterial antigens (Rappaport and Chase 1964, and Hirata *et al.* 1972a). A "loss" of some HL-A antigens from circulating lymphocytes after major surgery or irradiation (Bertrams *et al.* 1971) and a "change" in the HL-A type after blood transfusions have been claimed. A loss of an HL-A antigen during relapse in one patient with a lymphocytic malignancy has been noted (Seigler *et al.* 1971) and the lability of HL-A antigens in cell cultured has been shown (Dick *et al.* 1972). For reasons that are still unclear, relatively minor surgery without the use of blood or drugs (but involving general anesthesia) may produce temporary gains or deletions of antigens in the early postoperative period (White *et al.* 1972a). Exercise or alcohol comsumption could affect the expression of HL-A antigens (or influence the testing), thus showing the problems in HL-A typing (Zmijewski 1966, and Zmijewski *et al.* 1967). There have been reports showing that drugs can change the HL-A antigens (Butler and Rossen 1972, and Ben-David *et al.* 1973), although some reports were challenged (Russell *et al.* 1972b). Therefore, when tested, patients should not be taking medication, or if this is not possible, the influence of the medication upon HL-A typing must be assessed in separate investigations.

Most of the sera presently available for HL-A typing are weak. Anticomplementary activity can develop in these sera, particularly after prolonged storage, and reduce their cytotoxic effect.

Lymphocyte alloantibodies have been found in different dysgammaglobulinemic states (Waters *et al.* 1971). Three-quarters of the patients with lupus erythematosus as well as some patients with rheumatoid arthritis, pulmonary fibrosis, and myasthenia gravis have lymphocytotoxic antibodies (Mittal *et al.* 1970). Autoantibodies with sublytic or anticomplementary activity may give rise to a spurious correlation between HL-A typing and some diseases (Ceppellini 1971). Some antisera used for HL-A

typing may also have antibody to "disease-specific antigens," e.g., tumor- or virus-associated antigens. Moreover, the reaction of histocompatibility antibody with HL-A determinants on the surface of lymphocytes can be blocked nonspecifically by different substances (Hirata and Terasaki 1972b). Antibodies to "leukemia antigens," for example, might act synergistically with weak HL-A antibodies, producing false, positive cytotoxicity and therefore an apparent association between leukemia and HL-A antigens (Harris and Viza 1971). Additional HL-A cytotoxic reactions were found in cases of acute lymphocytic leukemia, possibly because of the formation of new antigens or of uncovering existing ones, that cross react with HL-A determinants (Dawey et al. 1974). In the case of apparent increased sensitivity of lymphocytes, for example in lepers (Escobar-Gutierrez et al. 1973), weak extra-HL-A antibody components often present in alloantisera may cause false, positive results leading to an apparent increase in antigen frequency. It is a wise precaution to confirm these results through family genotyping. In fact, the phenotype is only a handle for determining the genotype, which is more important with respect to the disease association (Bodmer 1973a).

To demonstrate an association between a disease and particular HL-A antigens, it is necessary to use a large panel of antisera, the specificity of which has been tested in several laboratories. Controls must be typed with the same antisera at the same time as the test samples. The use of cadavers as normal controls should be avoided, since it might give a false, high incidence of certain antigens (White et al. 1972a). It is better to repeat the tests at a later date and include further defined typing antisera as they become available. Defining the HL-A antigens of platelets, which can be done by a complement fixation test, could clarify some serological problems.

Statistical Errors. In comparing many different HL-A antigens, as are presently determined in most tissue typing laboratories, one would expect to find, by chance alone, at least one significant association. For example, if the frequency of 20 antigens in patients with a given disease is compared to their frequency in controls, even if none of the antigens is really associated with the disease one antigen will differ significantly at a 5% level when assessed by the *chi-square* test. Therefore, the usual statistical test cannot be used in such cases. To avoid this statistical problem (the so-called Bonferroni inequality), Bodmer suggested that the "p" value obtained by the *chi-square* test be multiplied by the number of antigens tested, e.g., the number of comparisons. Thus, with 20 comparisons, a true significance level of 5% would require a significance level of 0.25% with the usual statistical test (Bodmer 1973b). It is even better to demonstrate the same increased frequency of a particular antigen in two consecutive studies, i.e., make a pilot study to select the antigens with frequencies deviating from those of the controls and a large-scale prospective test in another group. In this latter, the association being looked for is stipulated a priori and not picked out as an extreme deviate. Confidence in a statistical deviation is strengthened if the distribution of antigens of one HL-A locus (*LA* or *FOUR*), taken as a whole, differs from the controls.

In many earlier studies concerning the association of HL-A with disease, the statistical problem described above was not considered. Hence, it has now become obvious that many published results are, in fact, not statistically valid. This statistical aspect is still sometimes negelected, as it has been suggested that the correction is too stringent and not necessary when only trends are sought (Takasugi et al. 1973). The

complexity of statistical analysis made the use of computers an integral part of tissue typing; however, the programs used still vary from one laboratory to another.

A proper analysis is sometimes difficult since many studies are performed on a small number of patients because some diseases are rare or it is difficult to find patients with distinctive clinical features. Studies of as few as 10 patients have been reported (Walford et al. 1970a and Schlessinger and Amos 1968) and these can be accepted only as pilot studies. It is very likely that only in diseases with a well recognized genetic component is it possible to obtain a high degree of association with the histocompatibility antigens in a small number of patients. A large number of patients must be tested especially in case of an association with a less common HL-A antigen. Another statistical bias is introduced by the fact that, in general, only positive studies are published. Only very recently it was proposed that all negative results be collected in an international registry to avoid duplicate work and save antisera (Svejgaard 1973a).

Immunological Considerations. The correlation found in animals between susceptibility to viral tumors and transplantation antigens stimulated the search for a correlation between HL-A antigens and malignant diseases of man. It is known, for example, that in addition to other factors, the susceptibility of mice to Friend leukemia virus is influenced by a gene linked to *H-2* (Lilly 1970). However, the *H-2* haplotype is not the sole determinant of susceptibility to viruses, but rather represents one of several genetic determinants of susceptibility. Several other genes, not linked to *H-2*, influence the susceptibility to Friend leukemia virus. Murine lymphocytic choriomeningitis virus infection is controlled, in part, by a dominant gene closely linked to *H-2* (Oldstone et al. 1973). A correlation between immune response to an autoantigen, disease severity, and histocompatibility type was shown in the case of murine thyroiditis (Vladutiu and Rose 1971).

In mice and guinea pigs specific *immune response* genes (*Ir* genes) linked to *histocompatibility* loci have been described. They are autosomal dominants and have a quantitative effect specific for the amino acid composition of the antigen, determining whether or not an individual is capable of eliciting an immune response to certain determinants (Benacerraf and McDevitt 1972, McDevitt 1973, and Gunther 1973). It has been established in mice that these genes are located in a chromosome region (*Ir* region) within the *H-2* complex. The *Ir* gene products are not known and several hypotheses have been proposed (Feldman 1973). The products could be (a) cell surface antigens that interact with typical immunoglobulin receptors and modify their function, or (b) antigen-specific receptors of thymus-deficient lymphocytes having a structure completely unrelated to the known immunoglobulins. The recent serological identification of *Ir* gene products (Hauptfeld et al. 1973, Götze et al. 1973, and David et al. 1974) could lead to a better understanding of the role of histocompatibility-linked *Ir* genes.

If lymphocytes from two different individuals are cultured together, they will stimulate each other, enlarge, and then divide. This mixed lymphocyte reaction (MLR) occurs in unrelated, *HL-A* identical individuals but has also been found in rare cases with lymphocytes from *HL-A* identical sibs (Yunis et al. 1971). From this finding, it appears that MRL is not a response to the serologically defined HL-A antigens, but a response to antigens controlled by at least one "*MLR*" or "*M*" locus closely linked to *HL-A* (Bach et al. 1972a). The function of this locus and its relationship to *Ir* genes are not understood.

The major histocompatibility region has serologically-defined (*SD*) and lympho-cyte-defined (*LD*) determinants (Bach *et al.* 1972b). The former can be identified by the usual serologic tests with agglutinating or cytotoxic antibodies, the latter by stimu-lation of lymphocytes in MLR. It has been suggested that the *Ir* gene products are the same as *LD* determinants in mice (Bach *et al.* 1972b). In human lymphocytes, *LD* determinants can be identified by using test cells that are homozygous for *LD* as well as for *SD* (Jersild *et al.* 1973b).

Disease Association. The many conditions in which an association with HL-A antigens has been sought (Table 1) can be divided into four groups. The first group includes infectious processes, such as infectious mononucleosis (Morris and Forbes 1971b), Yersinia arthritis (Aho *et al.* 1973), *H. influenzae* infections (Wisnant *et al.* 1971), streptococcal infections (Krain *et al.* 1973a), and poliomyelitis (Morris and Pietsch 1973b). The second group consists of neoplastic diseases, such as chorio-carcinoma (Lewis and Terasaki 1971, Morgensen *et al.* 1971, Ivaskova *et al.* 1969, Robinson *et al.* 1967, Amiel and Lebovici 1970, and Bagshawe and Lawler 1971); retinoblastoma (Bertrams *et al.* 1973a); breast carcinoma (Takasugi *et al.* 1973, Martz and Benacerraf 1973, Patel *et al.* 1972, and Cordon and James 1973b); lymphomas (Amiel 1967, Falk and Osoba 1971, Forbes and Morris 1972, Forbes and Morris 1970, Thorsby *et al.* 1971a, Kissmeyer-Nielsen *et al.* 1971b, Jeannet and Maguin 1971, Forbes and Morris 1971, Dick *et al.* 1972, Rege *et al.* 1972, Bertrams *et al.* 1972b, Coukell *et al.* 1971, Morris and Forbes 1971b, and Zervas *et al.* 1970); and leukemias (Walford *et al.* 1970a and Kourilsky *et al.* 1968b). The third group contains immuno-logic disorders that include autoimmune diseases, such as Hashimoto's thyroiditis (Roberts *et al.* 1973 and Bode *et al.* 1973); allergies, such as ragweed hypersensitivity (Marsh *et al.* 1973 and Levine *et al.* 1972); and other diseases with an immunologic pathogenesis, such as systemic lupus erythematosus (Grumet *et al.* 1971, Bitter *et al.* 1972, and Waters *et al.* 1971). Finally, the last group consists of diseases of unknown etiology, such as diabetes mellitus (Singal and Blajchman 1973, Finkelstein *et al.* 1972); ankylosing spondylitis (Schlosstein *et al.* 1973, Brewerton *et al.* 1973a, and Caffrey and Jarnes 1973); Reiter's disease (Woodrow 1973, Zachariae *et al.* 1973, Brewerton *et al.* 1973b, and Svejgaard *et al.* 1973b); and psoriasis (Krain *et al.* 1973a, White *et al.* 1972b, Russel *et al.* 1972a, and Svejgaard *et al.* 1973b).

Most of the disease associations appear to relate to antigens of the *FOUR* rather than the *LA* locus. The increased frequency of an HL-A antigen in a particular disease could have two possible explanations: either the disease process produced an increase in the relevant antigen or the antigen was present before the onset of the disease, re-flecting a heightened susceptibility or resistance to the disease. The second possibility is more likely since a quantitative variation of HL-A antigens in diseases has not been demonstrated so far. HL-A antigens showing negative associations (decreased fre-quency) are probably allelic with those showing positive associations (increased frequency). Negative association for the LA antigens can be explained, in part, in terms of the linkage disequilibrium between *LA* and *FOUR* locus antigens.

The biological mechanisms underlying the correlation between histocompatibility antigens and disease in animals have been discussed by Snell (1968) and in humans by McDevitt *et al.* (1972) and Dausset (1972a). Several mechanisms, not mutually exclu-sive, should be considered, one of which might be important in a particular disease.

1. Since HL-A antigens are present on the surface of many different cells, they

Table 1. Conditions in which an Association with HL-A Antigens was Investigated

Conditions	HL-A Antigens	Reference
Infectious mononucleosis	W 5	Morris and Forbes 1971b, Schiller and Davey 1973
Yersinia arthritis	HLA 27	Aho *et al.* 1973
Haemophilus influenzae infections	HLA 3, HLA 8, HLA 11	Wisnant *et al.* 1971
Severe streptococcal infections	HLA 13	Krain *et al.* 1973
Rheumatic fever	HLA 3	Falk *et al.* 1973
Leprosy	HLA 3	Escobar-Gutierrez *et al.* 1973, Thorsby *et al.* 1973
Malaria	none	Ceppellini 1973
Paralytic poliomyelitis	HLA 3, HLA 7	Morris and Pietsch 1973
Malignant melanoma	HLA 5	Clark *et al.* 1973, Van Wijk and Bouillene 1973, and Cordon 1973
Choriocarcinoma	HLA 2	Lewis and Terasaki 1971, Morgensen *et al.* 1971, Ivaskova *et al.* 1969, Robinson *et al.* 1967, Amiel 1970, Bagshawe and Lawler 1971
Retinoblastoma	HLA 12, W 5	Bertrams *et al.* 1973a
Breast carcinoma and other solid tumors	W 14, W 18, HLA 1, HLA 7, W 5	Takasugi *et al.* 1973, Martz and Benacerraf 1973, Patel *et al.* 1972, Cordon and James 1973
Hodgkin's disease and other lymphomas	HLA 1, HLA 8, W 15, W 18, W 5, HLA 11, HLA 3, HLA 5	Amiel 1967, Falk and Osoba 1971, Forbes and Morris 1972, Forbes and Morris 1970, Thorsby *et al.* 1971, Kissmeyer-Nielsen *et al.* 1971, Jeannet and Maguin 1971, Morris and Forbes 1971a, Bertrams *et al.* 1972, Coukell *et al.* 1971, Morris and Forbes 1971b, Zervas *et al.* 1970, Lawler 1973
Multiple myeloma	W 18	Bertrams *et al.* 1972b
Acute myeloid leukemia	HLA 8	Jeannet and Maguin 1971, Pegrum *et al.* 1970
Chronic myeloid leukemia	HLA 3, HLA 12	Degos *et al.* 1971, Kourilsky *et al.* 1968b
Acute lymphoblastic leukemia	HLA 1, HLA 2, HLA 3, HLA 9	Walford *et al.* 1970a, Thorsby *et al.* 1971a, Jeannet and Maguin 1971,

Table 1 *Continued*

Conditions	HL-A Antigens	Reference
		Lawler and Klondo 1971, Thorsby *et al.* 1969, Batchelor *et al.* 1971, Kourilsky *et al.* 1968a, Walford *et al.* 1971b, Kourilsky *et al.* 1968b
Chronic lymphoid leukemia	HLA 3, HLA 12 W 15	Schlessinger and Amos 1968, Jeannet and Maguin 1971, Degos *et al.* 1971, Walford *et al.* 1971b
Autoimmune thyroiditis	None	Roberts *et al.* 1973, Bode *et al.* 1973
Chronic active hepatitis	HLA 1, HLA 8	Mackay and Morris 1972
Graves' disease	HLA 8	Grumet *et al.* 1973
Ragweed allergy	HLA 7, HLA 1, HLA 8, HLA 3, HLA 5, HLA 9	Marsh *et al.* 1973, Levine *et al.* 1972
Atopic dermatitis	HLA 3, HLA 9	Krain and Terasaki 1973
Systemic lupus erythematosus	HLA 7, HLA 8, W 5, W 15	Grumet *et al.* 1971, Bitter *et al.* 1972, Mittal *et al.* 1970, Waters *et al.* 1971
Rheumatoid arthritis	W 10, HLA 27, HLA 13	Lies *et al.* 1972, Kueppers *et al.* 1972, Seignalet *et al.* 1972, Rachelefski *et al.* 1974
Chronic glomerulonephritis	HLA 2	Patel *et al.* 1969, Mickey *et al.* 1973
Myasthenia gravis	HLA 1, HLA 8	Pirskanen *et al.* 1972, Fritze *et al.* 1974, Behan *et al.* 1973
Multiple sclerosis	HLA 3, HLA 7, HLA 9, HLA 10	Jersild *et al.* 1973b, Bertrams *et al.* 1973b, Jersild *et al.* 1972a, Bertrams and Kuwert 1972, Naito *et al.* 1972, Jersild and Fog 1972b, Cazzullo and Smeraldi 1972
Pemphigus	HLA 13, HLA 10	Katz *et al.* 1973, Krain *et al.* 1973c
Celiac disease	HLA 8, HLA 1	McNeish *et al.* 1973, Katz *et al.* 1972, Falchuk *et al.* 1972, Stokes *et al.* 1972,

Table 1 *Continued*

Conditions	HL-A Antigens	Reference
		Stokes *et al.* 1973, Price 1973, Granditsch *et al.* 1973, Falchuk and Strober 1972
Dermatitis herpetiformis	HLA 8 (HLA 1)	Gebhard *et al.* 1973, Katz *et al.* 1972, White *et al.* 1973, Barnetson *et al.* 1973
Psoriasis	HLA 17, HLA 13	Krain *et al.* 1973a, White *et al.* 1972b, Russell *et al.* 1972a
Ankylosing spondylitis	HLA 27	Schlosstein *et al.* 1973, Brewerton *et al.* 1973a, Caffrey and Jarnes 1973
Reiter's disease	HLA 27	Woodrow, 1973, Zachariae *et al.* 1973, Brewerton *et al.* 1973c
Acute and chronic uveitis	HLA 27	Brewerton *et al.* 1973c, Ehlers *et al.* 1974, Mapstone and Woodrow 1974
Sarcoidosis	none	Kueppers *et al.* 1972, Hedfords and Möller 1973
Regional enteritis	none	Thorsby and Lie 1971b
Gout	none	Schlosstein *et al.* 1973
Diabetes mellitus	W 15	Singal and Blajchman 1973, Finkelstein *et al.* 1972
Bronchial asthma	HLA 1, HLA 27, HLA 1, HLA 8	Thorsby *et al.* 1971a
Cystic fibrosis	HLA 5, HLA 7	Walford *et al.* 1970b, Polymenidis *et al.* 1973
Down's syndrome	None	Harris *et al.* 1969
Isoagglutinin production	HLA 12, HLA 2, W 10	Brain 1972, Brain and Hammond 1974
Isoantibody to HLA 2	HLA 3	Morris 1973
Responsiveness to BCG	none ?	Amos *et al.* 1973, Ceppellini 1973
Behçet's disease	HLA 5	Ohno *et al.* 1973

may function as receptors capable of binding viruses or other substances of pathologic significance or may interact with such receptors. According to this hypothesis the susceptibility must be dominant. A receptor for the poliovirus, similar to or influenced by HL-A antigens, could exist, since patients with paralytic poliomyelitis have a higher incidence of HL-A 3 and HL-A 7 (Morris and Pietsch 1973b). Tissue culture studies suggest the possibility that the host's *HL-A* genes or genes closely linked to *HL-A* may

play a role in conditioning resistance to viral infection (Dausset *et al.* 1972b). Even though studies of avian leukosis gave some support to this hypothesis (Crittenden *et al.* 1970), there is no direct evidence for it in humans.

2. A particular virus, by a process of evolutionary adaptation designed to increase its infectious capacity, may share antigenic determinants with the histocompatibility antigens rendering the host unable to react immunologically against the virus, a phenomenon referred to as "molecular mimicry" (Snell 1968). The poliovirus, for example, could be chemically related to particular HL-A antigens. Therefore people having such transplantation antigens would not react immunologically against the virus and would thus be affected. The association of certain neoplasia with some HL-A antigens could be similarly explained, considering that these forms of neoplasia (e. g., leukemia or lymphoma) have a viral etiology. There is no evidence so far of a cross-reaction between HL-A antigens and viruses.

3. Genes controlling the HL-A antigens may be linked to *Ir* genes. The latter control the ability of the host to respond to the antigenic determinants of a particular virus or perhaps to viral-induced tumor antigens. A positive immune response would be associated with resistance to disease, and this should be dominantly controlled. Patients with acute lymphocytic leukemia (ALL) having HL-A 2 or HL-A 9 seem to survive longer than patients that do not have these antigens. It appears that HL-A 2 or HL-A 9 confer a resistance to ALL. This resistance could be due to an Ir gene linked to HL-A controlling the immune response to tumor-associated antigens (Rogentine *et al.* 1973 and Lawler *et al.* 1974). Individuals lacking such gene(s) would not mount an immune response and would be susceptible to the disease. The reverse situation is theoretically possible, i. e., people having such gene(s) could mount a strong immune response leading in some instances to production of immune complexes or to auto-immunity (e. g., systemic lupus erythematosus or chronic active hepatitis) or to an excess of IgE and to hypersensitivity states (e. g., ragweed allergy). Some Ir genes may code for the synthesis of facilitating antibodies which help the agressor. A strong immune response thus increases susceptibility, which is dominant (Dausset 1974). The reports of Marsh *et al.* (1973), Levine *et al.* (1972), and Buckley *et al.* (1973), strongly support the existence of *HL-A* linked human *Ir* genes.

The association between some HL-A antigens and the ability to respond to influenza vaccine in Hodgkin's disease and other lymphomas (Sybesma *et al.* 1972) or to measles antibody in multiple sclerosis (Jersild *et al.* 1973a) substantiates the association of HL-A antigens and immune responsiveness. The antigens HL-A 3 and HL-A 7, which occur with higher frequency in patients with multiple sclerosis and paralytic poliomyelitis, could be linked to an *Ir* gene determining the response to a viral infection of the central nervous system, e. g., the poliovirus in poliomyelitis and perhaps the measles virus in multiple sclerosis (Morris and Pietsch 1973b). Since the relative incidence of HL-A 3 in multiple sclerosis is higher than that of HL-A 7, a hypothetical *Ir* could exist between *LA* and *FOUR* loci.

It has been suggested that the *Ir* genes affecting the disease susceptibility may be more closely linked to (or identical with) the *MLR* locus which governs cellular interactions (Martz and Benacerraf 1973). Very recently Jersild *et al.* (1973b), using an MLR test, showed that a particular LD determinant, LD 7a, is more frequent in randomly selected multiple sclerosis patients than in controls. The association with LD 7a was much stronger than with HL-A 7 or HL-A 3. It seems that the increased

frequency of HL-A 3 and 7, which was found in other investigations (Bertrams *et al.* 1972, Jersild *et al.* 1972a, and Bertrams and Kuwert 1972) is secondary to increased frequency of LD 7a. These results could explain the inability to find an association between HL-A antigens and diseases, such as Hashimoto's thyroiditis, in which an immune mechanism plays a major pathogenic role (Roberts *et al.* 1973 and Bode *et al.* 1973). It may be that an association exists between this disease and particular LD determinants.

Bodmer has suggested that there may be a large number of genes in the HL-A region other than those determining the serologically detectable histocompatibility antigens, which either control synthesis of a particular class of differentiation antigens and/or control the synthesis of a class of recognizers (Bodmer 1972). He postulated the existence of a *"disease-susceptibility locus"* (*DSA*) in the *HL-A* region. The different associations found in different forms of a disease could be explained if there were, in fact, associations with different alleles at the *DSA* locus or with different *DS* loci, not all of which are necessarily closely linked to *HL-A*. However, such an association is found with diseases in which involvement of an immune response is not recognized. In these diseases it can be assumed that particular proteins, the synthesis of which are controlled by other genes linked to *HL-A* loci, play a role in pathogenesis. Such genes can control, for example, the synthesis of a receptor for gliadin in celiac disease. A strong correlation between celiac disease and HL-A 8 and HL-A 1 has been reported (Gebhard *et al.* 1973, McNeish *et al.* 1973, Falchuk *et al.* 1972a and b, Stokes *et al.* 1972, and Stokes *et al.* 1973).

Particular HL-A antigens have been associated with many diseases, suggesting the existence of similar pathogenic mechanisms, such as a disturbed immunologic response.

HL-A 8 has been associated with diseases such as systemic lupus erythematosus (Grumet *et al.* 1971); dermatis herpetiformis (Gebhard *et al.* 1973, Katz *et al.* 1972, White *et al.* 1973); celiac disease (Falchuk *et al.* 1972a, Stokes *et al.* 1972, Stokes *et al.* 1973, Price 1973, Granditsch *et al.* 1973, and McNeish *et al.* 1973); chronic active hepatitis (Mackay and Morris 1972); myasthenia gravis (Pirskanen *et al.* 1972, Fritze *et al.* 1973, and Behan *et al.* 1973); *H. influenzae* infections (Wisnant *et al.* 1971); asthma (Thorsby *et al.* 1971a); Hodgkin's disease (Kissmeyer-Nielsen *et al.* 1971b); and Graves' disease (Grumet *et al.* 1973). HL-A 8 also has been found with an increased frequency in strong responders to flagellin immunization and in patients who gave positive skin tests to mumps, tuberculin, Candida, and tricophytin (Morris 1973a), and it has been suggested that HL-A 1 and HL-A 8, probably as haplotypes, are associated with an exaggerated immune response to autoantigens thereby predisposing the development of autoimmune diseases. HL-A 27-positive individuals have also been shown to react in an unusual way to a variety of infective agents (Woodrow 1973). Other HL-A antigens have been associated with immune disturbances. Lymphocytes of healthy individuals with HL-A 3, 7 haplotype lack spontaneous cytotoxic activity. These individuals may have a genetic predisposition to an immunologic imbalance (Petranyi *et al.* 1974). HL-A 7 is less common in patients with hypersensitivity to brain antigen than in nonreactive patients with multiple sclerosis. Hence a correlation between a T cell-mediated aberration and HL-A 7 in patients with multiple sclerosis has been suggested (Finkelstein *et al.* 1974).

It is noteworthy that in some circumstances the *absence* of a particular HL-A

antigenic specificity might be a meaningful correlation. In patients with multiple sclerosis HL-A 2 and HL-A 12 have been decreased when compared to matched controls (Jersild et al. 1973c), and it has been considered that individuals who lack antigen W10 may produce antibodies that initiate demyelination (Naito et al. 1972).

A search has been undertaken for a correlation between HL-A antigens and diseases with strong genetic influence, such as psoriasis, or ankylosing spondylitis, and diseases without a known genetic influence. In view of the latest reports, there is no doubt that a definite correlation with HL-A antigens does exist in at least a few diseases, such as celiac disease, ankylosing spondylitis, chronic active hepatitis, psoriasis, multiple sclerosis, Reiter's disease and anterior uveitis.

In many of the diseases studied so far the etiology is unknown. Hence, there is difficulty in explaining the correlation between such diseases and HL-A antigens. It is not known at the present time whether illnesses such as leukemia or systemic lupus erythematosus have a viral etiology.

The genetic influences on many diseases is polygenic (multifactorial). Because of the polygenic control, susceptibility to a single specific disease entails an association with HL-A antigen that cannot be absolute but, at best, only statistical. It is obvious that the HL-A system is not an exclusive determinant of the disease. Other factors, either genetic and not linked to HL-A loci or environmental, must also play a role. In Hodgkin's disease, for instance, HL-A seems to contribute only one-thousandth of the causative factors (Ceppellini 1973). Only 8% of the males and 1% of the females with HL-A 27 would be expected to develop clinically apparent ankylosing spondylitis. In this case some other genes which govern the penetrance must exist since ankylosing spondylitis occurs only in a few relatives of patients. HL-A 27 is equally found in both sexes, therefore the association of HL-A 27 with ankylosing spondylitis cannot explain the 90% male preponderence.

The question arises as to why not all individuals with a particular disease have the same HL-A antigens. Assuming that Ir genes are involved in susceptibility to disease, the rather weak association between HL-A and a specific disease is understandable, since crossing over in an outbred population, such as the human population, has destroyed the association between HL-A and human Ir genes. As Walford pointed out, if we only did H-2 typing on complete outbred random leukemic mice, the correlation with H-2 would tend to be obscured (Walford 1971a). The HL-A antigens segregate precisely at a single locus in families, whereas the genetics of cancer susceptibility is not attributable to simple segregation. Therefore, a high association with HL-A antigens in cancer patients has not been found. It could be that non-HL-A related genes determine a "general" susceptibility to disease and HL-A has a modifying or quantitative influence (Walford et al. 1971b).

In animal experiments it was shown that the correlation between histocompatibility antigens and immune responsiveness can be revealed easier by using low doses of native antigens (Vaz and Levine 1970). Indeed, in allergic patients Marsh et al. (1973) found a linkage between HL-A 7 and sensitivity to a particular, low molecular weight, ragweed antigen, Ra 7. Exposure to this antigen is very low, i. e., the immunizing dose is small. In many diseases exposure to potential antigens is very high (for example, infectious diseases), therefore a correlation with HL-A antigens is difficult to demonstrate.

Conclusion

The question has been raised as to whether the correlation of HL-A antigens with various diseases is important enough to justify the continuously increasing number of reports dealing with this topic. Ceppellini (1973) pointed out recently, at an international meeting on genetics of the immune responsiveness, that "we have to avoid the game of chasing statistically significant associations which may have little biological and clinical relevance." Theoretically, such an association could explain the genetic polymorphism of the HL-A system. However, as stressed by Bodmer, most of the diseases studied so far are rare, occur late in life, or have little effect on viability or fertility. If associations were found with important infectious diseases, such as smallpox or cholera, that have or have had, in the past, a relatively high incidence, they could be of great significance in understanding the biological importance of the *HL-A* system (Bodmer 1972). By finding an association between HL-A antigens and a particular disease and assuming that *Ir* genes are responsible for this association, the specific antigen (viral, bacterial, tumor, autoantigen, etc.) must be found to which the response is controlled by the *Ir* genes. Therefore, the "HL-A associated diseases" might be used as a clue for the study of *Ir* genes in man. It is possible that the identification of alleles related to disease susceptibility in man may have to await improved techniques for their resolution at the *MLR* locus, i. e., increased availability of *LD* homozygous lymphocytes.

The association of the same HL-A antigen with several diseases such as HL-A 27 with ankylosing spondylitis and Reiter's disease, could mean that the diseases have a similar etiology, i.e. a particular agent may preferentially infect cells having the same HL-A antigen. The association of some diseases with particular HL-A antigens may have a significant adjunctive diagnostic value. In the case of difficult diagnoses, such as in some cases of ankylosing spondylitis, HL-A typing could help to establish the diagnosis. In this situation, the risk of having the disease appears to be 10 times higher in people with HL-A 27 than in the overall population (Schlosstein *et al.* 1973). Tissue typing might help differentiate acute Reiter's disease from gonococcal arthritis since virtually all cases of Reiter's disease have HL-A 27 in contrast to only 8% of the normal population (Morris *et al.* 1974a). In addition, HL-A 27 is useful in distinguishing between the arthropathies of inflammatory bowel disease. It also identifies a subgroup of patients at risk for developing spondylitis but not peripheral arthritis (Morris *et al.* 1974b). Typing families in whom the incidence of antigen-specific allergic diseases is high might serve to identify those members at risk for these diseases so that preventive measures might be instituted earlier. Patients with myasthenia gravis who have HL-A 3 should be monitored for developing thymomas (Fritze *et al.* 1974).

The association of HL-A and disease could also have a prognostic value. It is possible that children with HL-A 9 are less susceptible to acute lymphoblastic leukemia than children lacking this antigen. Furthermore, if they do develop the disease they have a better prognosis (Lawler *et al.* 1974). Finally, HL-A typing could influence the therapeutic approach in some diseases. Since the highest frequency of HL-A 8 has been found in myasthenia patients with thymic hyperplasia, it has been suggested that these patients would be good candidates for early thymectomy (Fritze *et al.* 1974).

The best correlation between transplantation antigens and susceptibility to disease has been found in inbred animals, but the clinical picture and the pathology of

disease is better documented in humans than in animals. Still, studies showing an association of HL-A antigens with particular diseases should be interpreted cautiously. If all possible pitfalls of determining such associations are avoided and the results are highly significant, the underlying physiological, biochemical, and immunogenetic aspects have to be considered. Further studies in other geographic areas, as well as testing a large number of patients, are important. Moreover, the association of some HL-A antigens with particular diseases may prove not to represent increased suscepti- bility to disease but rather an increased resistance to the disease once it has been ac- quired (Rogentine *et al.* 1973 and Lawler *et al.* 1974). It seems wise to emphasize associations between histocompatibility antigens and diseases with a firm genetic influ- ence or in which a disordered immunological response is established. It would be interesting to also look for a relationship of diseases with other well-defined loci, such as *Gm* and *InV*. Family studies are needed in many diseases in order to substantiate their association with HL-A antigens.

Looking for associations of diseases with particular LD determinants, which are demonstrated in mixed lymphocyte culture, is a new and promising field of investiga- tion. The very recent progress in identification of Ir gene products in animals (Haupt- feld *et al.* 1973, Götze *et al.* 1973, and David *et al.* 1974), as well as in the purification of HL-A antigens, (Billing *et al.* 1974), together with the discovery of new histocom- patibility antigens (Gelshore and Doughty 1973) will probably aid in seeking the cor- relation of HL-A antigens with diseases. Establishing a valid statistical association is only the first step. In elucidating the mechanisms of the association, many new facts and insights about the nature of disease will certainly emerge.

Acknowledgment

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