Terminology

Nomenclature for factors of the HL–A system *

After the Third Conference on Histocompatibility Testing, a Nomenclature Committee drawn from among specialists in tissue typing, immunology, and human genetics proposed a nomenclature for leucocyte antigens, which has become accepted internationally. The text of the memorandum drawn up by the Committee was published in the Bulletin of the World Health Organization *(1968,* **39,** *483–486). After the Fifth Workshop on Histocompatibility, the Nomenclature Committee*[1] *decided that it was necessary to revise the 1968 memorandum. The following is the text of the revised memorandum.*

Since the first human leucocyte isoantigens were described in the late 1950s, the number of leucocyte and platelet specificities defined by agglutination, complement fixation, and cytotoxicity techniques has been increasing. These factors are found on a variety of tissue cells and the possibility that they are histocompatibility antigens has been proposed. The definition of antigenic specificities and of genetic relationships among them was greatly facilitated by the introduction of computer analysis. Many leucocyte and platelet factors have been detected. The intricate relationships among them, evident from population and linkage studies, has led to the concept that most of these specificities belong to a single complex system. In this system, the specificities can be arranged in two segregant series and, within each series, each specificity behaves as if determined by one of a mutually exclusive set of alleles.

This major system was designated HL-A. The relevance of HL-A as an immunogenetic marker was confirmed by family studies combining serology, skin grafting, and lymphocyte culture techniques. The present memorandum concerns the nomenclature of specificities within the HL-A system and does not relate to other antigenic systems.

The definition of a histocompatibility antigen of the HL-A system passes through four stages. In the first, a new specificity is detected by a laboratory and given that laboratory's designation. Next, if this specificity is confirmed by several of the reference laboratories (see the Annex) it is given a provisional number preceded by the prefix W. In the third stage, when firm agreement has been reached by all the reference laboratories on the definition of this new specificity, an HL-A number can be designated. Finally, the fourth stage, which has not yet been reached, would allow the chemical confirmation of this HL-A specificity.

Since 1968, a number of specificities have been given HL-A numbers. The following ones remain relatively well defined: HL-A1, HL-A2, HL-A3, HL-A7, HL-A8, HL-A11, HL-A12, and HL-A13. Problems have arisen with HL-A9, which appears to represent a cross reactivity between two components, HL-A10 and HL-A5. The latter also seem to be associated with a number of cross-reacting specificities that are still difficult to disentangle in non-caucasoid populations.

Description of nomenclature

The use of subscripts, italics, lower-case letters, and similar devices is avoided for ease of composition, communication, and computation. In the 1968 memorandum[1] the Committee recommended that a distinct specificity should be designated by a number and that closely related but different specificities should be indicated by adding a figure after a full stop. However, the Committee has now decided that this notation should be abandoned as it implies a biological relationship between factors, which may not be correct. In future a new specificity that is part of a broader HL-A specificity will be given a new number by the Committee. The designation will be reported initially as a W specificity. For example, the two components of HL-A9 will now be designated W23 and W24 (Table 1), but HL-A9 will continue to be defined as the broader specificity. The assignment of W numbers that do not overlap with existing HL-A numbers allows for the possibility

* A French version will be published in a later issue of the *Bulletin.*

[1] See list of signatories on pages 661-662.

Table 1. New HL-A designations and representative equivalents

New designations	Representative equivalents
W16	U18, Da31 (included in U18), Ge12, Sa533, Te64, Ao81
W21	Da24, ET, ?M3, ?Te61
W23	HL-A9.1, Da27 (9'), Lc-12
W24	HL-A9.2, Da32 (9"), BIM
W25	HL-A10.1, To31, Da29 (10")
W26	HL-A10.2, To40, Da28 (10')
W29	W19.1, Ao77, Bt15, Da22, Ge33, Te63
W30	W19.3, Da25' (Da26), Lc-21, Te66
W31	W19.4, LAW, Da25' (Da33), Lc-26.1
W32	W19.5, Ao28, To30, Ge32, Te59

that, when an antigen to which a W number has been provisionally assigned becomes eligible for an HL-A number, it can keep the same number. Table 1 shows the specificities to which W numbers have been assigned and their equivalent terms. These assignments arose out of the Fifth International Histocompatibility Workshop. At present it is not possible to state to what degree these newer factors are important in matching donors and recipients of organ transplants. It seems likely that the definition of families of cross-reacting specificities will be important in this respect, but knowledge of the components of these cross-reacting groups is still incomplete.

The HL-A phenotype of an individual will be represented by the system symbol followed by the numbers corresponding to the defined factors, separated by a comma—e.g., HL-A1, 2, 7, 8. Where one of the factors has a W designation, the phenotype will be expressed as before, but the W prefix will appear before the factor—e.g., HL-A1, W23, 7, W16.

The genotype must be derived from family segregation analysis (or another means of genetic analysis) that identifies the two sets of factors controlled by the two homologous chromosomes. These sets, or haplotypes, are indicated by the factors that are inherited in coupling, separated by a comma. Thus, for the examples given above, the haplotypes could be HL-A1, 8 and HL-A2, 7, and HL-A1, W16 and HL-A, W23, 7, respectively. The genotype is indicated by the two haplotypes separated by an oblique stroke (solidus)—e.g., HL-A, 8/2, 7.

A series of serological factors, such as the HL-A specificities, are grouped into a system if the recombination fractions between their corresponding genetic determinants are small. The effective limit on these recombination fractions is set by the resolution of human pedigree studies and so is unlikely to be much less than 1%. A frequent, but not inevitable, consequence of such close linkage is association among the factors at the population level. Such association may vary from one population to another. The recognition of a new factor belonging to a system such as HL-A depends, therefore, not only on a population correlation analysis with established HL-A factors, but also on family studies. The families studied must be directly informative with respect to recombination involving the postulated new factor. The Committee recommended that, in order to be assigned to the HL-A system, a new factor should show no recombination among a total of at least 20 genetically informative children from at least 3 families. This makes interdependence between the new factor and the HL-A system unlikely, although it does not exclude comparatively loose linkage—for example, with a recombination fraction of about 10% at a probability level of 0.1. Further family studies showing recombination between HL-A factors at a level below 1%, or chemical evidence leading to an understanding of gene–antigen relationships, may justify subdividing the HL-A system into small genetic units in future.

Allocation of numbers

The following procedures are recommended for obtaining international designations for HL-A factors. Until certification is obtained, a local designation is appropriate; numbers preceded by the symbols HL-A or W should not be used.

Preliminary testing in laboratory of origin. The investigator should screen, on his own cell panel, sera suspected of defining new specificities, comparing them with antisera defining known HL-A specificities. In addition, panels including individuals from different race groups can be very helpful and their use where appropriate is recommended. The following steps are recommended:

1. The investigator should attempt to obtain more than one serum defining the supposed new specificity.

2. The reagents should be available in quantities of at least 200 ml. (Smaller quantities of high-titred

[1] *Bull. Wld Hlth Org.*, 1968, 39, 483-486.

serum may contain an equivalent amount of antibody.)

3. The reagents should give a reproducibility of at least 95% by a recognized technique designated by the investigator.

4. They should be monospecific or oligospecific on the basis of absorptions with at least 10 selected positive cells when retested on the immunizing donor or on at least 10 highly reactive cells. The use of cells that are known to have a blank allele of the appropriate series, as well as of cells that are known to be homozygous, will provide a more precise definition of a new specificity.

Certification

1. The sera should be tested on members of 3 or more genetically informative families containing at least 20 children and should show no recombination with HL-A factors.

2. When these criteria have been fulfilled, the evidence should be submitted to a WHO collaborating laboratory. The laboratory may supply the investigator with cells, fresh or frozen, from its own panel of characterized donors. Details of the procedure will be agreed upon by the investigator and the laboratory concerned.

3. Ultimately, the reagent must be shown to be operationally monospecific by absorption with, in general, cells from not fewer than 30 positive subjects if the frequency of reaction is greater than 15%, or from not fewer than 15 positive donors if the frequency is less than 15%.

4. If the specificity is confirmed as apparently new, verification should be obtained from a second collaborating laboratory.

5. All relevant data will then be considered by the Committee and, if the designation does not correspond to a previously designated factor, it will be given a W number.

Two sera can be considered to define the same specificity only if they give identical results when tested on a panel containing approximately 100 cells of which at least 10 should react positively and 10 negatively. Any discrepancies that exist on first testing should disappear on repeated testing or following absorption.

* * *

F. H. Allen, New York Blood Center, New York, N.Y., USA

D. B. Amos, Duke Medical Center, Durham, N.C., USA (*Chairman*)

J. R. Batchelor, Queen Victoria Hospital, East Grinstead, Sussex, England

W. F. Bodmer, University of Oxford, Oxford, England

R. Ceppellini, Institute of Medical Genetics, University of Turin, Italy

J. Dausset, Institut de Recherches sur les Maladies du Sang, Hôpital St-Louis, Paris, France

F. Kissmeyer-Nielsen, Aarhus Community Hospital, Aarhus, Denmark

P. J. Morris, University of Melbourne, Victoria, Australia (*Rapporteur*)

Rose Payne, Stanford University School of Medicine, Palo Alto, Calif., USA

J. J. van Rood, University of Leiden, Leiden, Netherlands

P. I. Terasaki, University of California School of Medicine, Los Angeles, Calif., USA

Z. Trnka, Basle Institute for Immunology, Basle, Switzerland (*Secretary*)

R. L. Walford, University of California School of Medicine, Los Angeles, Calif., USA

Annex

COLLABORATING LABORATORIES FOR LEUCOCYTE ANTIGEN TESTING

Professor D. B. Amos and Dr F. E. Ward, Department of Microbiology and Immunology, Duke University Medical Center, Durham, N.C., USA

Professor J. R. Batchelor, McIndoe Memorial Research Unit, Blond Laboratories, Queen Victoria Hospital, East Grinstead, Sussex, England

Professor W. F. Bodmer and Dr J. G. Bodmer, Genetics Laboratory, Department of Biochemistry, University of Oxford, Oxford, England

Professor R. Ceppellini, Centro Immunogenetica ed Istocompatibilità-CNR, c/o Institute of Medical Genetics, University of Turin, Turin, Italy

Professor J. Dausset and Dr J. Colombani, Institute for Research on Blood Diseases, Hôpital Saint-Louis, Paris, France

Dr P. Ivanyi, Institute of Experimental Biology and Genetics, Czechoslovak Academy of Sciences, Prague, Czechoslovakia

Dr M. Jeannet, Chief Medical Officer, Histocompatibility Laboratory, Geneva, Switzerland

Dr F. Kissmeyer-Nielsen, Blood Bank and Blood Grouping Laboratory, Aarhus Community Hospital, Aarhus, Denmark

Dr P. J. Morris, Tissue Transplantation Laboratories, Department of Surgery, University of Melbourne, The Royal Melbourne Hospital, Victoria, Australia

Dr Rose Payne, Dr C. Grumet, and Dr H. Perkins, Department of Medicine (Hematology), Stanford University School of Medicine, Palo Alto, Calif., USA

Dr J. J. van Rood, Department of Immunohaematology, University of Leiden, Leiden, Netherlands

Dr P. I. Terasaki, Department of Surgery, University of California School of Medicine, Los Angeles, Calif., USA

Dr R. L. Walford and Dr G. Smith, University of California School of Medicine, Los Angeles, Calif., USA

Dr C. P. Engelfriet and Dr J. J. van Loghem, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, Netherlands

---