INTERNAL MEDICINE GRAND ROUNDS

HLA IN CLINICAL MEDICINE

by

Peter Stastny

Department of Internal Medicine

(Transplantation Immunology Section)

The University of Texas Health Science Center at Dallas

October 23, 1975

INTRODUCTION

Originally of interest mainly in transplantation immunology the histocompatibility antigens (HLA) have rapidly drawn wider attention when it was recognized that alloantibodies detect structures concerned with a variety of cell membrane functions. From the point of view of the clinician, apart from the interest in biology, the important discovery was that histocompatibility antigens in man may be closely associated with the development of certain diseases. The best example is the association of the antigen HLA-B27 with predisposition to develop ankylosing spondylitis. Since 90% of the patients with ankylosing spondylitis carry this antigen, the test for B27 has rapidly entered medical practice as a diagnostic procedure. Marked increases in the frequency of HLA-B27 were found also in patients with Reiter's disease, in spondylitis associated with inflammatory bowel disease, in psoriasis with arthritis and in patients with acute anterior uveitis. As a result these conditions are now thought to be related in pathogenesis and perhaps also in etiology. A variety of other clinical conditions have been shown to have associations with histocompatibility genes. Included are ailments as diverse as gluten enteropathy, Graves' disease, juvenile diabetes, multiple sclerosis and rheumatoid arthritis. It is still early to fully evaluate the repercussions that these discoveries may have on clinical practice. Already they are providing new ways of looking at the classification of diseases and their pathogenesis. Undoubtedly they will prove useful in the areas of prognosis, therapy and prevention in a number of different clinical conditions.

BIOLOGY OF THE MAIN HISTOCOMPATIBILITY COMPLEX

Much has been written about the remarkable polymorphism of the histocompatibility antigens and the probable evolutionary pressures that led to their development and maintenance (1,2,3). Jerne (1) postulated that alloantigens serve to generate the whole diversity of receptors required for immunologic responses; Burnet (3) suggested that the major function of alloantigens is to protect against invasion by cells from other individuals; and Bodmer (2) found an explanation in the need for differentiation antigens and complementary receptors in the development of cell-cell interactions during early development of multi-cellular organisms.

Some of the functions presently controlled by the genes of the main histocompatibility complex are shown in Table 1. Certain antigens are widely held to function in cell-cell interactions. Among them are embryonic T/t antigens (4) which are controlled by a locus near to the mouse H-2 K region. They are expressed during embryonic development and appear to be rather important

TABLE 1

FUNCTIONS ASSOCIATED WITH THE MAIN HISTOCOMPATIBILITY CHROMOSOMAL REGION

1. Cell-cell interactions
   a) embryonic antigens (T/t)
   b) differentiation antigens (Tla, Ia)
   c) strong histocompatibility antigens (HLA-A, B and C)
2. Cell-mediated immunity
   a) T-cell receptors (in helper and effector T-cells)
   b) antigen presentation molecules
3. Antibody formation
   a) T-cell receptors
   b) helper factor (?)
   c) B-cell acceptor (?)
4. Specific immune response regulation (Ir)
5. Functions of complement factors
   a) classical pathway: C2, C4
   b) alternate pathway: factor B
6. Other cell membrane functions (hormone receptors?)

since the homozygous mutant T/T is incompatible with life at an early stage of the embryo. The differentiation antigens Tla, expressed in certain thymus derived lymphocytes (5) and the Ia antigens, expressed mainly in B-lymphocytes and certain other cells also belong to this group. Antigens equivalent to mouse Ia have recently been found in man (6,7). The main histocompatibility antigens (HLA-A, B and C) participate in cell interactions concerned with immunity. The role of H-2 antigens in cell mediated immunity in mice has been clearly established (8). The interaction of Ia and HLA molecules with two different subsets of allogeneic T cells is schematically represented in Figure 3, and will be discussed in more detail below. Another form of cell-cell interaction dependent on molecules of the histocompatibility complex is the T-B cell interaction in the course of antibody formation to thymus dependent antigens (9). However the exact nature of the cell interaction molecules is presently a matter of some debate (10).

The discovery of specific immune response (Ir) genes (11) which control the response to synthetic polymers of limited antigenicity or to larger proteins given in small amounts has provided an important stimulus to these investigations. Ir

genes are now also recognized in rhesus monkeys (12) and probably in man (13,14). The nature of the Ir gene products and their mechanism of action is a subject of intensive investigation at the present time (9,10).

Control of the second and the fourth components of complement (C2, C4) has been found to be linked to HLA. In addition the production of alleles of factor B of the alternate complement pathway is controlled by a gene located close to HLA (15,16).

Basal levels of cyclic AMP in the liver were found to segregate with H-2. Variation in the effect of glucagon, insulin and prostaglandins on adenyl cyclase activity in different mouse strains suggested an H-2 linked control of the interaction of hormones with the cell surface receptors (17).

REFERENCES

1. Jerne, N.K., The somatic generation of immune recognition. Eur. J. Immunol. *1:* 1, 1971.

2. Bodmer, W.F., Evolutionary significance of the HL-A system. Nature *237:* 139, 1972.

3. Burnet, F.M., Multiple polymorphism in relation to histocompatibility antigens. Nature *245:* 359, 1973.

4. Artzt, K., & Bennett, D. Analogies between embryonic (T/t) antigens and adult major histocompatibility (H-2) antigens. Nature *256:* 545, 1975.

5. Shreffler, D.C. & David, C.S. The H-2 major histocompatibility complex and the I immune response region: genetic variation, function and organization. Adv. Immunol. *20:* 125, 1975.

6. Winchester, R.J., Fu, S.M., Wernet, P. et al. Recognition by pregnancy serums of non-HL-A alloantigens selectively expressed on B lymphocytes. J. Exp. Med. *141:* 924, 1975.

7. Jones, E.A., Goodfellow, P.N., Bodmer, J.G., & Bodmer, W.F. Serological identification of HLA-linked human 'Ia-type' antigens. Nature *256:* 650, 1975.

8. Doherty, P.C. & Zinkernagel, R.M. A biological role for the major histocompatibility antigens. Lancet *1:* 1406, 1975.

9. Munro, A.J. & Taussig, M.J. Two genes in the major histocompatibility complex control immune response. Nature *256:* 103, 1975.

10. Katz, D.H. & Benacerraf, B. The function and interrelationships of T-cell receptors, Ir genes and other histocompatibiliby gene products. Transpl. Rev. *22:* 175, 1975.

11. McDevitt, H.O. & Benacerraf, B. Genetic control of specific immune responses in: Advances in Immunol. vol 11, F.J. Dixon and H.G. Kunkel, editors, Academic Press, New York, 1969, pp 31.

12. Dorf, M.E., Balner, H. & Benacerraf, B. Mapping of the immune response genes in the major histocompatibility complex of the rhesus monkey. J. Exp. Med. *142:* 673, 1975.

13. Buckley, C.W., Dorsey, F.C., Corley, R.B., Ralph, W.B., Woodbury, M.A. & Amos, O.B. HL-A-linked human immune-response genes. Proc. Nat. Acad. Sci. *70:* 2157, 1973.

14. Haverkorn, M.J., Hofman, B., Masurel, N. & van Rood, J.J. HL-A linked genetic control of immune response in man. Transpl. Rev. *22:*120, 1975.

15. Allen, F.H. Linkage of HL-A and GBG. Vox Sang. *27:*382, 1974.

16. Teisberg, P., Olaisen, B., Gedde-Dahl, T. & Thorsby, F. On the localization of the Gb locus within the MHS region of chromosome No. 6. Tissue Antigens *5*: 257, 1975.

17. Meruelo, D. & Edidin, M. Modulation of hormonal effects on adenyl cyclase by the histocompatibility-2 (H-2) locus. Fed. Proc. *34:* 979, 1975 (Abst).

GENETIC ORGANIZATION AND CHEMISTRY OF HLA

The main histocompatibility region is located on the sixth human chromosome (20,21). This HLA chromosomal region (18) is depicted in Figure 1, in which the loci are designated by letters A,B,C,D, according to the new nomenclature. Three loci (A,B,C) control the expression of antigens found in all nucleated cells which are easily detected by complement dependent cytotoxicity. They are called HLA-A (previously LA, First, or SD-1), HLA-B (previously Four, Second, or SD-2) and HLA-C (previously AJ or Third). HLA-D is the locus for determinants that produce strong mixed lymphocyte culture (MLC) stimulation (previously called MLR-S, LD-1 or LAD-1). Also shown in Figure 1, is the Bf locus which codes for allotypes of the B factor of the properdin system (15,16). Each HLA chromosome can code for only 1 of 19 HLA-A alleles and 1 of 20 HLA-B alleles (18). The prefix W before some antigen numbers stands for "workshop" and is used to indicate temporary status and that there may exist some difficulties in definition with available reagents. All the known alleles for the HLA-C and HLA-D loci are of this type. It should be stressed that HLA-D is different from the other three loci in

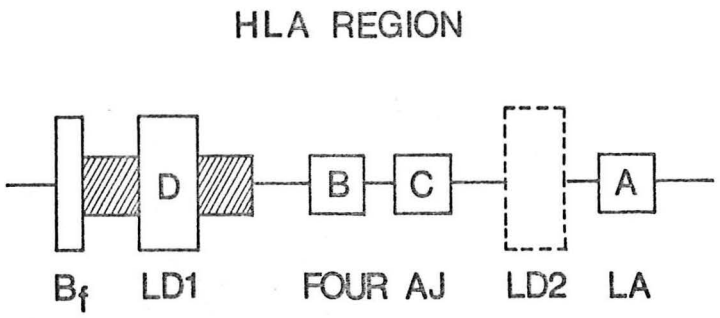

FIGURE 1. *The HLA chromosomal region of the sixth human chromosome.* The loci are identified as HLA-A, HLA-B, HLA-C. The older names (LA, Four and AJ) are given below. HLA-D is the locus that codes for determinants that produce strong stimulation in mixed lymphocyte cultures (MLC). Bf codes for alleles of factor B of the properdin system; a locus for the second component of complement (not shown) is thought to be very near. The crosshatched area represents the equivalent of the I region where immune response genes are presumed to be located.

that it codes for antigens expressed mainly in B-cells, which can at present be identified only by a mixed lymphocyte culture procedure. Alleles of the weaker MLC-locus (labeled LD-2 in Figure 1) have not yet been characterized.

The chemical structure of the HLA molecule (Figure 2) has been compared to that of immunoglobulin (10). It is a glycoprotein which consists of heavy polypeptide chains (MW 44,000) which carry the HLA antigenic determinants and small polypeptide chains (MW 12,000) identified as B-2-microglobulin. The heavy chains are cleaved by papain generating units of 34,000 daltons.

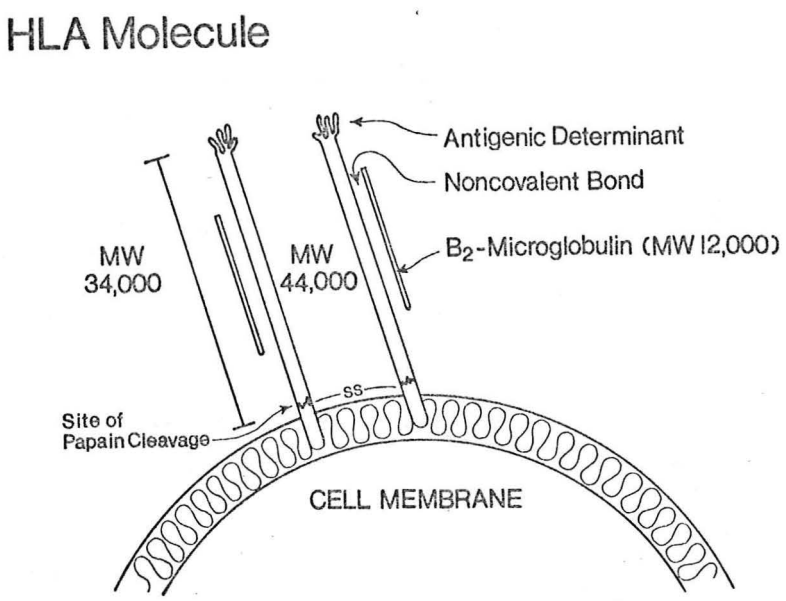

FIGURE 2. *The HLA Molecule.* HLA is a glycoprotein. The carbohydrate portion is not shown. The protein consists of two kinds of polypeptide chains: Heavy chains (44,000 daltons) which contain the antigenic determinant and a light chains identified as β-2-microglobulin (12,000 daltons).

The molecules appear to be arranged in dimeric form and are linked by a disulfide bond. The structural genes for the production of the heavy chains of the HLA molecules are located in the HLA chromosomal region of the 6th human chromosome (20,21). The gene coding for the synthesis of beta-2-microglobulin however, is located on chromosome number 15 (22). Certain antigens expressed mainly in B-lymphocytes probably coded by HLA-D or loci adjacent to it (hatched area in Figure 1, comparable to the I region in the mouse and rhesus monkey) do not appear to contain B-2- microglobulin. These antigens have been called Ia (for I region associated) in the mouse and will presently be called the same in man (6,7) until a better terminology can be developed.

The alleles of the four HLA loci are shown in Table 2. The main changes decided upon by the nomenclature committee this year (18) consisted of renaming the loci by letters following HLA; renaming the specificities W5 to BW35, and BW10 to W40; the dropping of the W prefix for antigens 14, 18, 27, 28, 29; and the addition of many new alleles on the basis of the results collected during the sixth workshop.

TABLE 2

HLA LOCI AND ALLELES

HLA-A		HLA-B		HLA-C	HLA-D
A1	AW23	B5	BW15	CW1	DW1
A2	AW24	B7	BW16	CW2	DW2
A3	AW25	B8	BW17	CW3	DW3
A9	AW26	B12	BW21	CW4	DW4
A10	AW30	B13	BW22	CW5	DW5
A11	AW31	B14	BW35		DW6
A28	AW32	B18	BW37		
A29	AW33	B27	BW38		
	AW34		BW39		
	AW36		BW40		
	AW43		BW41		
			BW42		

REFERENCES

18. WHO-IUIS HLA Nomenclature Committee for factors of the HLA system, in Histocompatibility Testing 1975, in press.

19. Strominger, J.L., Cresswell, P., Grey, H., et al. The immunoglobulin-like structure of human histocompatibility antigens. Transpl. Rev. *21:* 126, 1974.

20. Jongsma, A., Somerln, H.V., Westerneed et al. Localization of genes on human chromosomes by studies of human-chinese hamster somatic cell hybrids. Humangenetik *20:* 195, 1973.

21. Lamm, L.U., Friedrich, U., Petersen, G.B. et al. Assignment of the major histocompatibility complex to chromosome no. 6 in a family with pericentric inversion. Hum. Hered. *24:* 273, 1974.

22. Goodfellow, P.N., Jones, E.A., van Heyningen, V., et al. The β_2 - microglobulin gene is on chromosome 15 and not in the HL-A region. Nature *254:* 267, 1975.

ROLE OF HLA AND Ia MOLECULES IN CELL MEDIATED IMMUNITY

When human (23) or mouse (24) lymphocytes are stimulated *in vitro* different products of the HLA region seem to be involved in the sensitization phase (MLC) and in the effector phase, cell mediated lympholysis, (CML) of the allogeneic reaction. On the responder side it appears that at least two separate sub-populations of T-cells (Figure 3) are involved (25,26). The allogeneic stimulating cell presents one kind of determinant (Ia) to the T1 lymphocytes and another (HLA-A,B or C) to the T2 lymphocytes of the responder population. The T1 cells activated by the allogeneic I region molecules produce a helper factor. It acts on the T2 cell leading to differentiation and development of effector killer cells of cell mediated immunity. In testing for this, killer cells are allowed to interact with chromium labeled target cells which present on their surface the same HLA determinants as were present during sensitization. It can be shown that the T2 lymphocytes have become cytotoxic and cause chromium release from such targets. T1 and T2 percursor lymphocytes differentiate prior to and independently of antigenic exposure (25,26) and can be identified in mice by the presence on their surface of specific Ly antigens. It has also been shown that histocompatibility region molecules play similar roles in the course of the immune response to chemical and viral antigens. Of particular significance are experiments that showed that H-2 compatibility is required for destruction of target cells infected with ectromelia virus (27), lymphocytic choriomeningitis virus (28) and vaccinia (29). The requirement is for compatibility at the H-2 (K or D) loci and

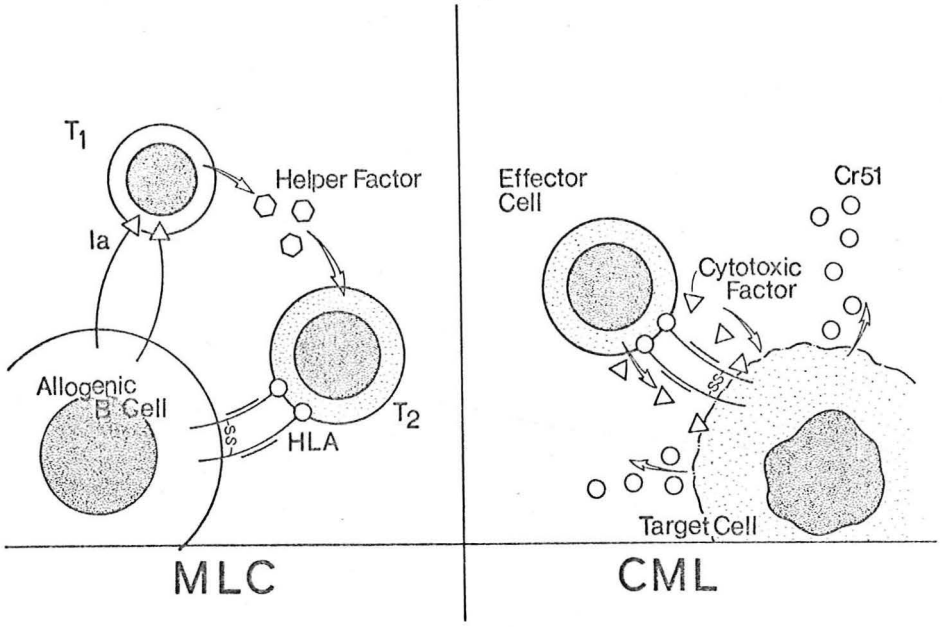

FIGURE 3. *Generation of cytotoxic killer cells of cell mediated immunity in the reaction to allogeneic cells.* MLC = mixed lymphocyte culture or sensitization phase; CML = cell mediated lympholysis. This figure is an interpretation of the role of Ia and HLA molecules in the stimulation and triggering of helper T-cells (Tl) and effector T-cells (T2) of cell mediated immunity. For more detail see text.

as Forman has recently shown (30) with trinitrophenyl modified targets, is not due to a separate event requiring histocompatibility but to the specificity of the immune process generated. An interpretation of the mechanism involved is shown in Figure 4. The sensitizing agent is an antigen combined with the HLA molecule on the surface of an autologous macrophage. This selects effector cells responding only to the same combination. Neither histocompatible target cell without antigen, nor the target cell with antigen but of a different HLA type can serve effectively. When

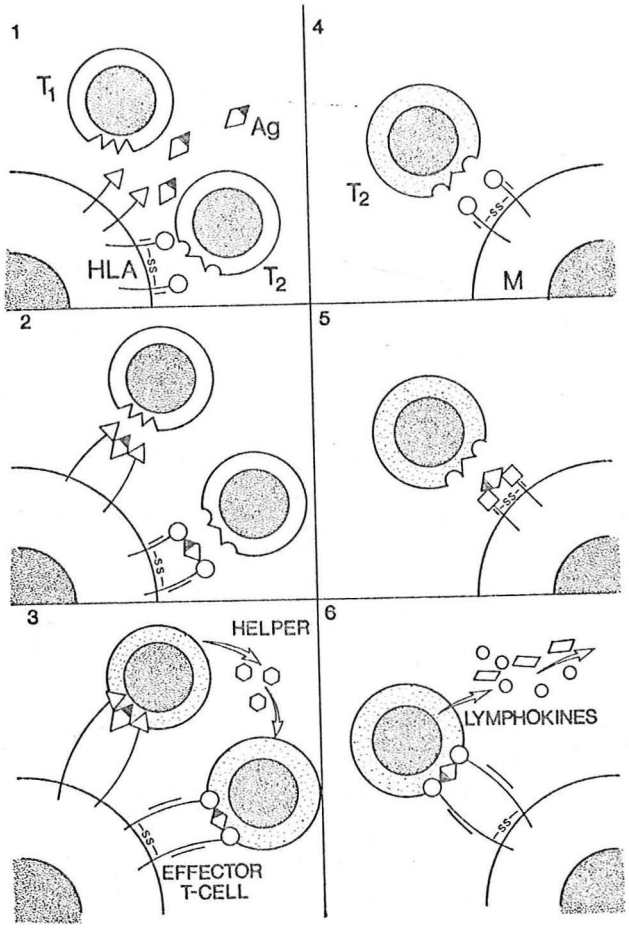

FIGURE 4. *Role of HLA (H-2)* in the immune response to virus infected or TNP modified target cells. The effector cell is sensitized to HLA plus antigen, it is triggered only by target cells that have these same determinants. For more detail see text.

both the HLA and the antigen are the same as those originally presented the killer cell is triggered. Somewhat similar histocompatibility requirements exist in the cooperation between T and B cells in the course of the humoral antibody response (31).

Because of the role in the immune response and in other cell functions the possibility of development of alleles in the histocompatibility region that would lead to predisposition for disease was considered likely. Such associations were rapidly found in experimental animals and the implications have been extensively reviewed (32,33,34,35).

REFERENCES

23. Eijsvoogel, V.P., Riadu Bois, C.J.M., Melief, W.P. et al. Lymphocyte activation and destruction *in vitro* in relation to MLC and HL-A. Transpl. Proc. *5:* 415, 1973.

24. Schendel, D.J. & Bach, F.H. Genetic control of cell-mediated lympholysis in mouse. J. Exp. Med. *140:* 1534, 1974.

25. Cantor, H. & Boyse, E.A. Functional subclasses of T lymphocytes bearing different Ly antigens I. The generation of functionally distinct T-cell subclasses in a differentiative process independent of antigen. J. Exp. Med. *141:* 1376, 1975.

26. Cantor, H. & Boyse, E.A. Functional subclasses of T lymphocytes bearing different Ly antigens II. Cooperation between subclasses of Ly+ cells in the generation of killer activity. J. Exp. Med. *141:* 1390, 1975.

27. Gardner, I., Bowers, N.A. & Blanden, R.V. Cell-mediated cytotoxicity against ectromelia virus-infected target cells. III. Role of the H-2 gene complex. Eur. J. Immunol. *4:* 63, 1974.

28. Zinkernagel, R.M. & Doherty, P.C. H-2 compatibility requirement for T-cell mediated lysis of target cells infected with lymphocytic choriomeningitis virus. Different cytotoxic specificities are associated with structures coded for in H-2 K or H-2 D. J. Exp. Med. *141:* 1427, 1975.

29. Koszinowski, V. & Ertl, H. Lysis mediated by T cells and restricted by H-2 antigen of target cells infected with vaccinia virus. Nature *255:* 552, 1975.

30. Forman, J., On the role of the H-2 histocompatibility complex in determining the specificity of cytotoxic effector cell sensitized against trinitrophenyl-modified targets. J. Exp. Med. *142:* 403, 1975.

31. Katz, D.H., Hamaoka, T. & Benacerraf, B. Cell interaction between histoincompatible T and B lymphocytes. II. Failure of physiologic cooperative interactions between T and B lymphocytes from allogeneic donor strains in humoral response to hapten-protein conjugates. J. Exp. Med. *137:* 1405, 1973.

32. McDevitt, H.O. & Bodmer, W.F., HLA ,immune response genes, and disease. Lancet *1:* 1269, 1974.

33. Dausset, J., Degos, L. & Hors, J. The association of the HL-A antigens with diseases. Clin. Immunol. Immunopathol. *3:* 127, 1974.

34. Svejgaard, A., & co-workers. HL-A and disease assocations - A survey. Transplan. Rev. *22:* 3, 1975.

35. Rood, J.J. van, Hooff, J.P. van, & Keuning, J.J. Disease predisposition, immune responsiveness and the fine structure of the HL-A supergene. Transplan. Rev. *22:* 75, 1975.

DISEASES ASSOCIATED WITH HLA-B27

HLA-B27 is an allele of the B locus which is highly cross-reactive with B7, but can be well differentiated from it with available reagents. Until the 6th International Histocompatibility Workshop it was called W27. The W indicating a temporary status was dropped in July, 1975. HLA-B27 is an antigen of relatively low frequency. It was found in 9% of the Caucasian control population typed in Dallas; in 2% of Black Americans and in 10% of Mexican-Americans typed (Table 3).

TABLE 3

DISEASES ASSOCIATED WITH HLA-B27

Clinical Condition	Combined Frequency (%)	Number of Subjects Studied	References
Normal Controls	9	537*	(36)
Ankylosing Spondylitis	90	192	(36,37,38,39)
Reiter's Disease	79	143	(36,39,42,43,44)
Reiter's after Yersinia, Salmonella Shigella infections	76	59	(45,46,47,48)

*From HLA typing of random Caucasian donors in Dallas; the frequencies were 2% in 206 Black-Americans and 10% in 50 Mexican-Americans.

DISEASES ASSOCIATED WITH HLA-B27 Cont'd

Clinical Condition	Combined Frequency (%) Studied	Number of Subjects	References
Inflammatory Bowel Disease with Spondylitis	73	26	(49,50)
Psoriasis with Arthritis	34	100	(36,49,51)
Psoriasis with Spondylitis	50	52	(36,49,51)
Acute anterior uveitis	56	126	(52,53,54)

The frequency of B27 is markedly increased in patients with *ankylosing spondylitis*. The combined frequency from several reports was 90%. This is the strongest HLA association found thus far and suggests that linkage with this histocompatibility antigen must be related to the pathogenesis and perhaps also to the etiology of ankylosing spondylitis. Although both the disease and the B27 antigen are more frequent in Caucasians ankylosing spondylitis is found also in other populations and interestingly the linkage with B27 is maintained. In Japanese, where B27 was almost completely absent in normal controls, 18 subjects who carried the B27 antigen all had ankylosing spondylitis (40). The overall frequency of B27 in this group of Japanese patients with ankylosing spondylitis was 67% compared to 0% in controls. In Caucasians of course B27 is found in many individuals who do not have ankylosing spondylitis indicating that other factors must be involved. It is possible however, that the frequency of ankylosing spondylitis may be under estimated. In a study recently reported random B27 positive donors and matched controls were selected in a tissue typing laboratory and questionnaires were sent to determine the frequency of symptoms and other manifestations suggestive of spondylitis. Twenty-two of the supposedly normal B27 positive individuals were found to have back pain and x-ray changes. It is possible that low grade unrecognized ankylosing spondylitis may be much more frequent than was previously believed.

Reiter's disease classically consists of a triad of arthritis, urethritis and conjunctivitis. Involvement of the spine and of the sacroiliac joints is common and may be very similar to ankylosing spondylitis. Frequency of HLA-B27 in patients with Reiter's disease was found to be close to 80% (Table 3). Non-specific urethritis is a common accompaniment of Reiter's disease, but patients with non-specific urethritis only, did not show an increase of B27. A syndrome very similar to Reiter's disease may develop following intestinal infection with *yersinia enterocolitica, salmonella* or *shigella*. In each case after an episode of dysentery the patients develop arthritis and mucous membrane lesions. Follow-up of such patients has shown a remarkable increase in the frequency of HLA-B27 (Table 3). Thus it appears that the B27 antigen signals the existence of a predisposition to develop arthritis and spondylitis after such infections.

A small number of patients with *ulcerative colitis* and with *Crohn's disease* developed ankylosing spondylitis. The frequency of B27 in patients with inflammatory bowel disease in general was not increased but in those individuals who developed spondylitis the frequency was 73% (Table 3).

Psoriasis is a disease often noted to be increased in families. Patients with psoriasis have been shown to have an increased frequency of the HLA antigens B13, BW17 and BW37. This will be discussed below. Arthritis may occur in certain patients with psoriasis. It is often seen in patients with fingernail psoriasis and tends to involve the distal phalangeal joints. A small number of patients develop spondylitis. There are also similarities between pustular psoriasis and keratodermia of Reiter's disease. HLA-B27 was found in 34% of patients with psoriasis and arthritis, and in 50% of psoriatic patients developing spondylitis (Table 3).

Acute anterior uveitis is an inflammatory condition of unknown cause limited to the anterior portion of the eye. It may be idiopathic or associated with certain systemic diseases. The most common being ankylosing spondylitis and Reiter's disease. It is therefore of interest to investigate the frequency of HLA-B27 in these patients. It was found to be 56% (Table 3).

Thus a number of clinical conditions known for some time to have certain features in common are now clearly grouped together by their association with the same HLA antigen. Already the test for B27 is being used by rheumatologists to confirm the diagnosis in suspected cases of ankylosing spondylitis or of Reiter's disease.

In the course of the past year our laboratory has received frequent requests for typing of patients suspected of having ankylosing spondylitis, Reiter's disease or psoriasis with arthritis. In our material the frequency of HLA-B27 was 96% in ankylosing spondylitis, 81% in Reiter's disease and 54% in patients with psoriasis and arthritis (Table 4). It is interesting to compare these values with frequencies of 12% in adults with rheumatoid arthritis and 15% in patients with juvenile rheumatoid

TABLE 4

HLA-B27 IN NORMAL INDIVIDUALS AND IN PATIENTS WITH VARIOUS RHEUMATIC DISEASES STUDIED IN DALLAS*

Diagnosis	Number Tested	HLA-B27 Positive Number	Percent
Normal Controls	793	59	7
Akylosing Spondylitis	24	23	96
Reiter's Disease	32	26	81
Psoriasis with Arthritis	11	6	54
Rheumatoid Arthritis	50	6	12
Juvenile Rheumatoid Arthritis	47	7	15

*Stastny, 1975, unpublished.

arthritis. Although HLA-B27 may be increased in children with spondylitis, the overall frequency of B27 in juvenile RA does not seem to show a significant deviation (95,96).

REFERENCES

36. Stastny, P., 1975, unpublished.

37. Brewerton, D.A., Caffrey, M., Hart, F.D., James, D.C.O., Nicholls, A. & Sturrock, R.D. Ankylosing spondylitis and HL-A 27. Lancet *1:* 904, 1973.

38. Schlosstein, L., Terasaki, P.I., Bluestone, R. & Pearson, C.M. Association of an HL-A antigen, W27, with ankylosing spondylitis. New Engl. J. Med. *288:* 704, 1973.

39. Amor, B., Feldman, J.L., Delbarre, F., et al. The HL-A antigen W27. A genetic link between ankylosing spondylitis and Reiter's syndrome. New Engl. J. Med. *290:* 572, 1974.

40. Sonozaki, H., Seki, H., Chang, S. et al. Human lymphocyte antigen, HL-A 27, in Japanese patients with ankylosing spondylitis. Tissue Antigens *5:* 131, 1975.

41. Calin, A. & Fries, J. An extraordinarily high prevalence of "ankylosing spondylitis" (AS) in W27 positive males and females. A controlled study. Arthr. Rheum. *18:*390, 1975 (Abst).

42. Woodrow, J.C. HL-A 27 and Reiter's syndrome. Lancet *2:* 671, 1973.

43. Brewerton, D.A., Caffrey, M., Nicholls, A., Walters, D., Oates, J.K. & James D.C.O. Reiter's disease and HL-A 27. Lancet *2:* 996, 1973.

44. Morris, R., Metzger, A.L., Bluestone, R. & Terasaki, P.I. HL-A W27 - A clue to the diagnosis and pathogenesis of Reiter's syndrome. New Engl. J. Med. *290:* 554, 1974.

45. Zachariae, H., Fries, J., Graudal et al. Reiter's disease and the histocompatibility antigen HL-A 27. Scand J. Rheum. *4:* 13, 1975.

46. Aho, K., Ahvonen, P., Lassus, A. et al . HL-A 27 in reactive arthritis: a study of yersinia arthritis and Reiter's syndrome. Arthr. Rheum. *17:* 521, 1974.

47. Fries, J. & Svejgaard, A. Salmonella arthritis and HL-A 27. Lancet *1:* 1350, 1974.

48. Calin, A. & Fries, J.F. Epidemic Reiter's syndrome. Genetics and environment. Arthr. Rheum. *18:* 390, 1975 (Abst).

49. Brewerton, D.A., Caffrey, M., Nicholls, A., Walters, D., & James, D.C.O. HL-A 27 and arthropathies associated with ulcerative colitis and psoriasis. Lancet *1:* 956, 1974.

50. Morris, R.I., Metzger, A.L., Bluestone, R.& Terasaki, P.I. HL-A-W27-A useful discriminator in the arthropathies of inflammatory bowel disease. New Engl. J. Med. *290:* 1117, 1974.

51. Metzger, A.L., Morris, R.I., Bluestone, R. & Terasaki, P.I. HL-A W27 in psoriatic arthropathy. Arthr. Rheum. *18:* 111, 1975.

52. Brewerton, D.A., Caffrey, M., Nicholls, A., Walters, D. & James, D.C.O. Acute anterior uveitis and HL-A 27. Lancet *2:* 994, 1973.

53. Ehlerhes, N., Kissmeyer-Nielsen, F., Kjerbye, K.E. & Lamm, L.U. HL-A 27 in acute and chronic uveitis. Lancet *1:* 99, 1974.

54. Mapstone, R. & Woodrow, J.C. Acute anterior uveitis and HL-A 27. Lancet *1:* 681, 1974.

DISEASES ASSOCIATED WITH HLA-B8

HLA-B8 is a more frequent antigen in Caucasians, it was present in 26% (Table 5). It is rare in Africans and in American Indians and its presence in Black-American and Mexican-American populations in Dallas in probably due to the presence of Caucasian genes. HLA-B8 is in strong linkage disequilibrium with HLA-A1 and with the MLC allele DW3. Typing for HLA-D is very new and information about HLA-D locus alleles in patients is rather limited. Already it appears however, that some diseases initially thought to be associated with HLA-B8 actually have stronger associations with HLA-DW3 (Figure 5). This appears to

TABLE 5

DISEASES ASSOCIATED WITH HLA-B8

Clinical Condition	Combined Frequency (%)	Number of Subjects Studied	References
Normal Controls	26	537*	(36)
Celiac Disease	79	126	(55,56,57)
Dermatitis Herpetiformis	62	89	(60,61,62)
Myasthenia Gravis	50	236	(65,66,67,68)
Chronic Active Hepatitis	66	58	(69,70,71)

*From HLA typing of random Caucasian donors in Dallas; the frequencies were 12% in 206 Black-Americans and 18% in 50 Mexican-Americans.

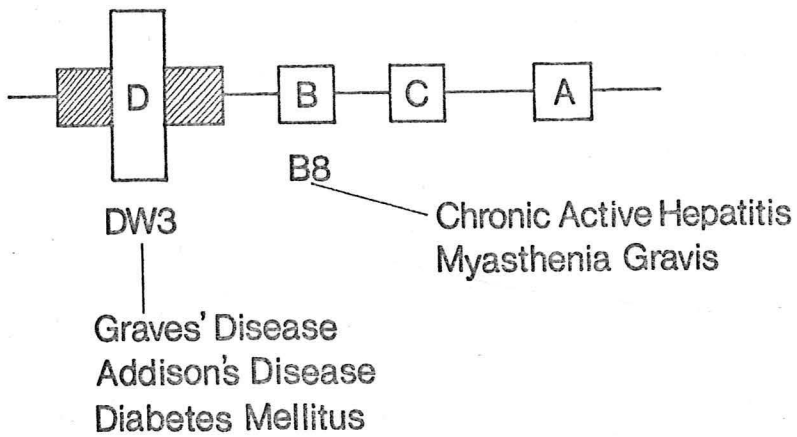

FIGURE 5. *Diseases associated with HLA-B8 and with HLA-DW3.* In some diseases the strongest association is HLA-B8, in others it seems to be HLA-DW3.

be true in Grave's disease, Addison's disease and diabetes mellitus of the juvenile insulin dependent type. On the other hand chronic active hepatitis and myasthenia gravis seem to have the strongest association with HLA-B8.

Among the diseases associated with this group of histocompatibility antigens celiac disease and dermatitis herpetiformis are most interesting (Figure 6). Celiac disease is the cause of a malabsorption syndrome with pathologic changes in the small intestine, dermatitis herpetiformis produces a skin rash with granular deposits of immunoglobulin A in the dermal papillae (64).

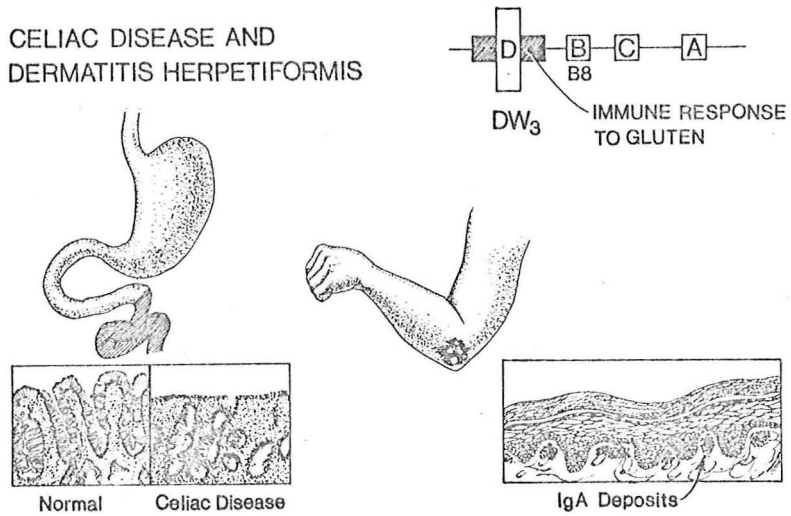

FIGURE 6. *HLA association in Celiac disease and dermatitis herpetiformis.* Possible linkage to a locus between HLA-B8 and HLA-DW3 responsible for the immune response to gluten.

The link between the two diseases seems to be the clinical response to withdrawal of gluten from the diet. In fact patients with both conditions have been shown to produce antibodies to a componenttof gluten. It seems reasonable that an immune response to gluten is involved in the pathogenesis. Both diseases have a similar linkage with the HLA chromosome. HLA-B8 was increased to 79% in patients with Celiac disease and to 62% in dermatitis herpetiformis (Table 5). In a small group a similar increase in the frequency of HLA-DW3 was found (35). It was postulated therefore that the primary association may be not B8 or DW3 but a locus between the two responsible for control of the immune response. The region adjacent to the strong mixed lymphocyte culture loci have been shown to contain immune response (Ir) genes in mice and in rhesus monkeys (11,12).

Myasthenia gravis is a disease well known to be associated with development of abnormal antibodies and tumors of the thymus. Recent evidence suggests that the defect in neuromuscular transmission that causes the symptoms may be due to presence of autoantibodies reacting with acetycholine receptors. The frequency of HLA-B8 in patients with myasthenia gravis was found to be twice that of normal controls. The information available suggests that this is the primary association but further work will be needed to rule out the possibility of a stronger association with an adjacent locus concerned with the immune response.

Chronic active hepatitis of the type which is not associated with hepatitis B virus has been found to be frequently associated with HLA-B8. The combined frequency was 66% (Table 5). A recent publication suggests that homozygosity for HLA-B8 was common in patients with chronic active hepatitis and that the primary association was B8 and not DW3 (71).

REFERENCES

55. Falchuk, Z.M., Rogentine, G.N. & Strober, W. Predominance of histocompatibility antigen HL-A 8 in patients with fluten-sensitive enteropathy. J. Clin. Invest. *51:* 1602, 1972.

56. Stokes, P.L., Asquith, P., Holmes G.K.T. et al. Inheritance and influence of histocompatibility (HL-A) antigen in adult coeliac disease. Gut. *14:* 627, 1973.

57. Albert, E.D., Harnes, K., Wank, R. et al. Segregation analysis of HL-A antigens and haplotypes in 50 families of patients with coeliac disease. Transpl. Proc. *5:*1785, 1973.

58. Scott, B.B., Swinburne, M.L., Rajob, S.M. & Losonsky, M.S. HL-A 8 and the immune response to gluten. Lancet *2:* 374, 1974.

59. Platz, P., Doniach, D., Rog, T. et al. LD typing and disease. Histocompatibility Testing, 1975 (in press).

60. White, A.G., Barnetson, R. St. C., De Costa, J.A.G. et al. The incidence of HL-A antigens in dermatitis herpetiformis. Brit. J. Derm. *89:* 133, 1973.

61. Katz, S.I., Falchuk, E.M., Dahl, M.V. et al. HL-A 8 a genetic link between dermatitis herpetiformis and gluten-sensitive enteropathy. J. Clin. Invest. *51:* 2977, 1972.

62. Gebhard, R.L., Katz, S.I., Marks, J., Shuster, S., Trapani, R.J., Rogentine, G.N. & Strober, W. HL-A antigen type and small-intestinal disease in dermatitis herpetiformis. Lancet *2:* 760, 1973.

63. Fry, L., Seah, P.P., Riches, D.J., Hoffbrand, A.V. Clearance of skin lesions in dermatitis herpetiformis after gluten withdrawal. Lancet *1:* 288, 1973.

64. Fry, L. & Seah, P.P. Dermatitis herpetiformis, in Immunological aspects of skin diseases, L. Fry and P.P. Seah, editors, J. Wiley and Sons, New york, 1974, pp 22.

65. Pirskanen, R., Tiilikainen, A., Hokkanen, E. Histocompatibility (HLA) antigens associated with myasthenia gravis. Ann Clin. Res. *4:* 304, 1972.

66. Feltkamp, T.E.N., Berg-Loonen, P.M. van der, Nijenhuis, L.E. et al. Myasthenia gravis, auto-antibodies and HL-A antigens. Brit. Med. J. *1:*131, 1974.

67. Fritze, D., Herrmann, C., Naeim, F., Smith, G.S. & Walford, R.L. HL-A antigens in myasthenia gravis. Lancet *1:*240, 1974.

68. Säfwenberg, J., Lindblom, J.B. & Osterman, P.O. HL-A frequencies in patients with myasthenia gravis. Tissue Antigens *3:* 465, 1973.

69. Mackay, I.R. & Morris, P.J. Association of autoimmune active chronic hepatitis with HL-A 1, 8. Lancet *2:* 793, 1972.

70. Bertrams, J., Reis, H.E., Kuwert, E. & Selmair, H. Hepatitis associated antigen (HAA), HL-A antigens and auto-lymphotoxins (CoCoCy) in chronic aggressive and chronic persistent hepatitis. Z. Immun. Forsch. *146:* 300, 1974.

71. Page, A.R., Sharp, H.L., Greenberg, L.J., Yunis, E.J. Genetic analysis of patients with chronic active hepatitis. J. Clin. Invest. *56:* 530, 1975.

DISEASES ASSOCIATED WITH HLA-D LOCUS ALLELES

Testing for HLA-D locus alleles is possible by performing mixed lymphocyte cultures with homozygous typing cells. The HLA-D locus was investigated for the first time in this way in the 6th International Histocompatibility Workshop during which the presently known alleles were defined (72). The normal values given in Table 6, are based on pooled workshop data. Some of the HLA-D locus alleles have strong linkage with HLA-B locus alleles including DW1 with HLA-DW35, DW2 with B7 and DW3 with B8.

In early studies, *multiple sclerosis* was found to have associations with HLA-A3 and B7. The strongest association however appears to be with DW2 (Figure 7), in three separate studies. The combined frequency of DW2 was 56% in multiple sclerosis compared to 15% in controls. It is probable that the linkage between the histocompatibility antigens is the cause of the apparent association with the other two loci (Figure 7). The presence of DW2 in patients

TABLE 6

DISEASES ASSOCIATED WITH HLA-D LOCUS ALLELES

Clinical Condition	Frequency (%)	Number Studied	References
HLA-DW2 (LD-7a)			
Normal Controls	15	171	(72)
Multiple Sclerosis	56	105	(73,74)
C2 Deficiency	83	6	(75,76)
HLA-DW3 (LD-8a)			
Normal Controls	16	171	(71)
Graves' Disease	54	26	(80,81)
Juvenile Diabetes	50	42	(82)
Addison's Disease	70	30	(82)

with multiple sclerosis has been associated with a more rapid rate of progression of the disease (73). It is often speculated that the etiology of multiple sclerosis may be related to a virus. The association with DW2 may represent linkage with an immune response gene important in handling this infection.

A *deficiency in the second component of complement* has been observed in rare patients suffering from systemic or discoid lupus erythematosus, glomerulonephritis, polyarteritis polymyositis and juvenile RA. Family studies have shown that patients lacking C2 are homozygous for a gene which in the heterozygous relatives produces about half the normal amount of C2 protein. Tissue culture experiments have shown that monocytes from patients with the genetic defect do not synthesize the protein (77). Inheritance of the C2 defective gene has been shown to be linked to the inheritance of HLA in families. The HLA haplotype A10, B18 was found in several C2 deficient subjects but other antigens were also found. Subsequently it was observed that unrelated patients with C2 deficiency did not stimulate each other in mixed lymphocyte cultures. The common HLA-D allele has been identified as DW2 and has been found to be present in 5 out of 6 involved families (Table 6). A number of other genetic abnormalities of

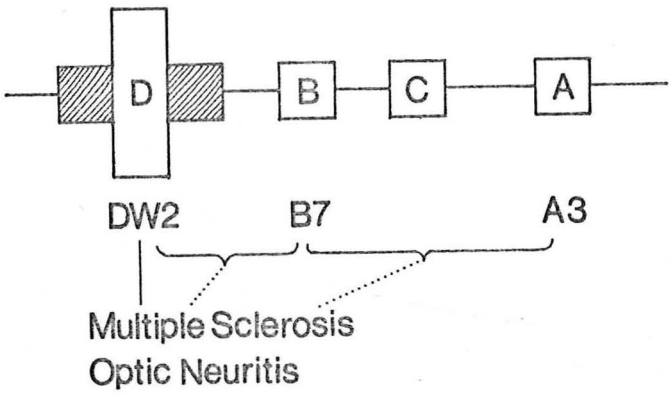

FIGURE 7. *HLA association in multiple sclerosis.* The strongest association is with HLA-DW2. The increased frequency of HLA-B7 and HLA-A3 may be due to the normal linkage between these histocompatibility alleles.

the complement system which may be associated with disease have been described (78). At least one other, the fourth component of complement is also controlled by genes linked to HLA (79). The nature of the link between C2 deficiency, HLA and the connective tissue-like diseases in these individuals is at present unknown. One possibility is that the complement defect itself predisposes to persistence of an infectious agent. A more likely explanation is that the link is through another locus near the complement deficiency gene.

HLA-DW3 is in linkage disequilibrium with HLA-B8. The frequency of DW3 among 171 individuals studied during the 6th Inter-

national Workshop was 16% (Table 6). B8 and DW3 seem to be involved in various pathologic conditions. The thyroid, the adrenal, the testicles, the islet cells of the pancreas and the gastric mucosa may be involved in autoimmune reactions. The hallmark in this group of diseases is the production of organ specific autoantibodies.

In the case of the thyroid, a relationship between *Graves' disease* and histocompatibility antigens has been found in several studies which showed an increase in the frequency of HLA-B8. In two recent series in which DW3 was also tested it was found that the D-locus allele showed the stronger association (Table 6). The pathogenesis of Graves'disease is obscure. A correlation between histocompatibility antigens and thyroid autoantibodies has not been found. Such correlations have been reported in the two other diseases that belong to this group. Islet cell antibodies in patients with juvenile diabetes and antiadrenal antibodies in patients with idiopathic Addison's disease did correlate with the presence of HLA antigen B8. In both conditions the strongest association is with the antigen DW3. It was 50% in juvenile diabetes, and 70% in patients with Addison's disease (Table 6).

In addition to association with HLA-B8 and HLA-DW3 juvenile diabetes was also reported to be associated with HLA-BW15. Patients having both B8 and BW15 appear to have a higher chance of developing insulin dependent diabetes, suggesting that the two traits have an additive affect and therefore probably operate through separate mechanisms. It has been suggested that HLA-B8 and DW3 influence the development of diabetes through an immune response mechanism (34). Islet cell antibodies have been demonstrated (87). In other experiments it was shown that HLA-BW15 may be associated with sub-normal insulin production in response to glucose infusion (34). It is tempting to speculate that this could be related to the action of HLA linked cell membrane hormone receptors (17), but information is not yet available.

HLA-DW4 was characterized by five LD typing cells during the 6th International Histocompatibility Workshop. One of them came from a Dallas patient with rheumatoid arthritis. The frequency of DW4 in the population studied in the workshop was 16%. In the local series of 54 normal individuals it was 11% (Table 7). Several reports failed to show abnormal distribution of HLA-A and HLA-B antigens in patients with rheumatoid arthritis. However when the alleles of the HLA-D locus were examined several patients with rheumatoid arthritis were found to be HLA-D locus homozygous (88). The LD determinant characterized in these cells has been identified as HLA-DW4. The frequency of DW4 in adult patients with *rheumatoid arthritis* was 72% (Table 7). In a group of children with *juvenile rheumatoid arthritis* the frequency of DW4 was found to be 32%, much less than in adults with rheumatoid arthritis but significantly more than in normal controls (90). Juvenile rheumatoid arthritis may well be a heterogeneous group. When the patients having the pauciarticular form of juvenile RA were excluded from the analysis, the frequency of HLA-DW4 rose and

TABLE 7

HLA-DW4 IN NORMAL INDIVIDUALS
AND IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

Diagnosis	Number Tested	HLA-DW4 Positive Number	Percent
Normal Controls[1]	171	27	16
[2]	54	6	11
Adult RA[2]	44	32	72
Juvenile RA[3]	38	12	32

[1] From Sixth International Workshop (71).
[2] From Stastny, 1975 (88,89).
[3] From Stastny & Fink, 1975 (90).

came close to the frequency found in adults.

There is some debate about the role of genetic factors in rheumatoid arthritis. Results of one survey suggested that environmental factors played the major role. In other studies a genetic influence was suggested (97,98,99).

REFERENCES

72. Thorsby, E. & Piazza, A. Joint report from the Sixth International Histocompatibility Workshop Conference II. Typing for the HLA-D (LD-1 or MLC) determinants, in Histocompatibility Testing 1975, in press.

73. Jersild, C., Fog, T., Hansen, G.S., Thompsen, M., Svejgaard, A., & Dupont, B. Histocompatibility determinants in multiple sclerosis, with special reference to clinical course. Lancet *2:* 1221, 1973.

74. Jersild, C., Dupont, B., Fog, T. Platz, P.J. & Svejgaard, A. Histocompatibility determinants in multiple sclerosis. Transpl. Rev. *22:* 148, 1975.

75. Fu, S.M., Stern, R., Kunkel, H.G. et al. Mixed lymphocyte culture determinants and C2 deficiency: LD-7a associated with C2 deficiency in four families. J. Exp. Med. *142:* 495, 1975.

76. Friend, P.S., Handwerger, B.O., Kim, Y., Michael, H.F. & Yunis, E.J. C2 deficiency in man. Genetic relationship to a mixed lymphocyte reaction determinant (7a)., in press.

77. Einstein, L.P., Heper, C.A., Bloch, K.J. et al. Biosynthetic defect in monocytes from human beings with genetic deficiency of the second component of complement. New Engl. J. Med. *292:* 1169, 1975.

78. Stroud, R.M. Genetic abnormalities of the complement system of man associated with disease. Transpl. Proc. *6:* 59, 1974.

79. Rittner, C.H., Hauptmann, G., Grosshaus, E. & Mayer, S. Linkage between HL-A (major histocompatibility complex) and genes controlling the synthesis of the fourth component of complement, in Histocompatibility Testing 1975, in press.

80. Thorsby, E., Segaard, E., Solem, J.H., Kornsted, L. The frequency of major histocompatibility antigens (SD & LD) in thyrotoxicosis. Tissue Antigens *6:* 54, 1975.

81. McMichael, A.J., Sasazuki, T., Grumet, F.C., Payne, R. & McDevitt, H.O. An HL-A 8 associated LD antigen in patients with Graves' disease, in Histocompatibility Testing 1975, in press.

82. Thomsen, M., Platz, P. Ortved Andersen, O, et al. MLC typing in juvenile diabetes mellitus and idiopathic Addison's disease. Transpl. Rev. *22:* 125, 1975.

83. Singal, D.P. & Blajchman, M.A. Histocompatibility (HL-A) antigens, lymphocytotoxic antibodies and tissue antibodies in patients with diabetes mellitus. Diabetes *22:* 429, 1973.

84. Cudworth, A.G. & Woodrow, J.C. HL-A system and diabetes mellitus. Diabetes *24:* 345, 1975.

85. Nerup, J., Platz, P., Andersen, D.O. et al. HL-A antigens in diabetes mellitus. Lancet *2:* 864, 1974.

86. Nelson, P.G., Pyke, D.A., Cudworth, A.G., Woodrow, J.L., Batchelor, F.J. Histocompatibility antigens in diabetic identical twins. Lancet *2:* 193, 1975.

87. Bottazzo, G.F., Florin-Christensen, A., Doniach, D. Islet-

cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet *2:* 1279, 1974.

HISTOCOMPATIBILITY ANTIGEN ASSOCIATIONS IN OTHER DISEASES

Psoriasis has been found to have associations with three different HLA-B locus alleles (Table 8), HLA-B13, BW17 and BW37. It appears that the relative risk is not increased in subjects having two of these antigens compared to those who have only one. Thus they do not seem to have an additive effect. Therefore their expression is probably dominant and they may act through the same mechanism (102). The presence of HLA-B27 in patients having psoriasis with arthritis and psoriasis associated with spondylitis has been discussed above.

Two other diseases are listed in Table 8. They are *pemphigus* with an association with HLA-B13 and *Behcet's disease* with a reported association with HLA-B5. The information comes from single reports based on studies of small numbers of patients which will have to be confirmed.

Many other diseases have been looked at. Of particular interest have been malignancies in view of the strong association of histocompatibility with development of leukemia in mice. In humans however thus far studies in neoplastic diseases have been disappointing. One of the more interesting reports is that of an association of an HLA-B locus antigen found almost exclusively in orientals, in patients with nasopharingeal carcinoma. The HLA antigen has been characterized in a second laboratory (106) and other studies of this disease association should be forth-

TABLE 8 HISTOCOMPATIBILITY ANTIGEN ASSOCIATIONS IN OTHER DISEASES

HLA Antigen	Frequency (%)	Number Studied	Normal Frequency (%)	References
		PSORIASIS		
B13	16	420	4	(100,101,102)
BW17	30	420	7	(100,101,102)
BW37	9	220	1	(102)
		PEMPHIGUS		
B13	28	18*	4	(103)
		BEHCET'S		
B5	71	21*	31	(104)

*Needs to be confirmed.

coming. HLA associations have been studied extensively in patients with Hodgkin's disease (107) but the overall results in 523 patients evaluated during the 5th International Histocompatibility Workshop have been inconclusive (108.)

Reports of HLA associations in patients with systemic lupus erythematosus were among the earliest to appear in the literature (109,110) but have not been confirmed in subsequent studies (111,112). There are technical problems in typing lymphocytes that may be coated by autoantibodies. Black patients with both systemic and discoid lupus erythematosus have been studied in Dallas and have not shown any significant deviations in the distribution of HLA-A and HLA-B alleles. HLA-D locus studies have not yet been performed, they may be technically difficult because of the presence of lymphocyte antibodies and the frequent use of high doses of immunosuppressive drugs.

REFERENCES

88. Stastny, P. Mixed lymphocyte culture typing cells from patients with rheumatoid arthritis. Tissue Antigens *4:* 571-579, 1974.

89. Stastny, P. MLC determinants associated with rheumatoid arthritis. In Histocompatibility Testing 1975, in press.

90. Stastny, P. & Fink, C. Mixed lymphocyte culture (MLC) and HL-A antigens in children with rheumatoid arthritis. Arthr. Rheum. *18:* 428, 1975 (Abst).

91. Lies, R.B., Messner, R.D. & Troup, G.M. Histocompatibility antigens in rheumatoid arthritis. Arth. Rheum. *15:*524, 1972.

92. Seignalet, J., Clot, J., Sany, J. & Serre, H. HL-A antigens in rheumatoid arthritis. Vox Sang. *23:* 468, 1972.

93. Brackertz, D., Mueller-Eckhardt, Ch., Heinrich, D., Kueppers, F., Schulz, G. & Dretschmer, V. Histocompatibility antigens of patients with rheumatoid arthritis. Z. Immun. Forsch. *146:* 108, 1973.

94. Nyulassy, S., Ravingerova, G., Zvarova, E. & Buc, M. HL-A antigens in rheumatoid arthritis. Lancet *1:* 450, 1974.

95. Rachelefsky, G.S., Terasaki, P.I., Katz, R. & Stiehm, E.R. Increased prevalence of W27 in juvenile rheumatoid arthritis. New Engl. J. Med. *290:* 892, 1974.

96. Gibson, D.J., Carpenter, C.B., Stillman, J., Schur, P.H. Re-examination of histocompatibility antigens found in patients with juvenile rheumatoid arthritis. New Engl. J. Med. *293:* 636, 1975.

97. O'Brien, W.M. The genetics of rheumatoid arthritis. Clin. Exp. Immunol.*2:* 785, 1967.

98. Bennett, P.H. & Bench, T.A. The genetics of rheumatoid arthritis in: Population studies of the rheumatic diseases. P.H. Bennett and P.H.N. Wood, eds. Excerpta Medica Foundation, New York, 1968.

99. Lawrence, J. S. & Wood, P.H.N. Genetic influences in rheumatoid arthritis in Rheumatic Diseases J.J.R. Duthie and W.R.M. Alexander, eds. The Williams & Wilkins Co., Baltimore, 1968, pp 20-28.

100. Russel, T.J., Schultes, L.H. & Kuban, D.J. Histocompatibility (HL-A) antigens associated with psoriasis. New Engl. J. Med. *287:* 738, 1972.

101. White, S.H., Newcomer, V.D., Mickey, M.R. & Terasaki, P.I. Disturbance of HL-A antigen frequency in psoriasis. New Engl. J. Med. *287:* 740, 1972.

102. Svejgaard, A., Staub-Nielsen, L., Svejgaard, E. et al. HL-A antigens in psoriasis-population and family studies. Brit. J. Dermatol. *91:* 145, 1974.

103. Katz, S.I., Dahl, M.V., Penneys, N., et al . HL-A antigens in pemphigus. Arch. Dermatol. *108:* 53, 1973.

104. Ohno, S., Hoki, K., Suguira, S. et al. HL-A 5 and Behcet's disease. Lancet *2:* 1383, 1973.

105. Simons, M.J., Wee, G.B., Chan, S.H. & Shanmugaratnam, K. Probable identification of an HL-A second-locus antigen associated with a high risk of nasopharyngeal carcinoma. Lancet *1:* 142, 1975.

106. Payne, R., Radvany, R. & Grumet, C. A new second locus HL-A antigen in linkage disequilibrium with HL-A 2 in Cantonese Chinese. Tissue Antigens *5:* 69, 1975.

107. Bodmer, W.F. Genetic factors in Hodgkin's disease: association with a disease susceptibility locus (DSA) in the HL-A region. Nat. Canc. Inst. Monograph *36:* 127, 1973.

108. Morris, P.J., Lawler, S., Oliver, R.T. HL-A and Hodgkin's disease, in Histocompatibility Testing 1972, Munskgaard Copenhagen, 1973 pp 669.

109. Waters, H., Donrad, P., Walford, R.L. The distribution of HL-A histocompatibility factors and genes in patients with systemic lupus erythematosus. Tissue Antigens *1:* 68, 1971.

110. Grumet, F.C., Conkel, A., Bodmer, J.G. et al. Histocompatibility (HL-A) antigens associated with systemic lupus erythematosus. A possible genetic predisposition to disease. New Engl. J. Med. *285:* 193, 1971.

111. Arnett, F.C., Bias, W.B., Schulman, L.E. HL-A antigens in systemic lupus erythematosus (SLE). Arthr. Rheum. *15:* 428, 1972.

112. Kissmeyer-Nielsen, Kjerbye, K.E., Andersen, E., Halberg, P. HL-A antigens in systemic lupus erythematosus. Transpl. Rev. *22:* 164, 1975.

113. Stastny, P. The distribution of HL-A antigens in Black patients with systemic lupus erythematosus (SLE).Arthr. Rheum. *15:* 454, 1972. (Abst.)

114. Prystowski, S.D., Gilliam, J.N., Stastny, P. & Herndon, J.H. Immunologic studies in discoid lupus erythematosus. Clin. Res. *22:* 332, 1974 (Abst.).

CONCLUSIONS

The origins of the HLA chromosomal region are traced to the development of signals and recognition molecules for primitive cell-cell interactions. Posterior evolution led to the utilization of this system in most of cellular immunity, certain complement functions and perhaps also functions of cell membrane associated hormone receptors. A striking characteristic of these systems is their ability of creating and maintaining a large variety of alleles (polymorphism) all of which seem to function. Some variations must of course exist and the possibilities for disease predisposition are obvious.

The search for disease associations has rapidly produced some evidence. These studies have revealed the existence of HLA linked factors of susceptibility for development of various clinical conditions. Most of these are multigenic and environmental factors play an important role. Different regions of the HLA chromosome may be involved and the genetic influence appears to be expressed in a variety of ways. In the case of juvenile diabetes association with two different alleles of the same locus appears to have an additive effect suggesting that they operate through different mechanisms. In psoriasis three different antigens may be involved but no additive effects have been observed. The study of associations between histocompatibility antigens and disease may provide new insight into mechanisms and pathogenesis. It is a method of probing that goes beyond the explanations of classical immunology. It is difficult to know how far it will lead. It is likely to make major contributions. In some instances the associations are so strong that HLA has already moved into bedside and office practice as a diagnostic test. It will be possible to group diseases on the basis of having similar predisposing factors such as HLA-B27

diseases, HLA-B8 diseases, HLA-DW4 diseases, etc. As more is learned about these associations some of them may become of prognostic significance as seems to be the case in multiple sclerosis where it was reported that HLA-DW2 is associated with more rapid clinical progression. In other situations it may turn out that HLA genes are markers of relative resistance, as has been postulated in Hodgkin's disease and certain forms of leukemia. It also is possible that HLA may serve as an indicator of response to certain modes of therapy. Family members carrying the predisposing genes may be identified and perhaps preventive measures taken. These might include occupational or vocationsl counseling, avoidance of exposure to predisposing causes and perhaps even development of resistance in predisposed hosts by specific vaccination or other forms of preventive therapy.