CONTINUING MEDICAL EDUCATION

BIOLOGICAL AND CLINICAL SIGNIFICANCE OF THE HLA SYSTEM

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The HLA associations reported so far have implications in diagnosis, prognosis and prophylaxis for a few of the diseases and in several cases, they have helped to clarify disease heterogeneity. However, the area where a full consensus is yet to be achieved is regarding the mechanism by which these disease associations with HLA antigens work. Numerous investigators have discussed various possible mechanisms in the light of individual diseases. In general, diseases associated with HLA class-I antigens may in some way involve cytotoxic T-lymphocytes whereas those more strongly associated with HLA class-II antigens (—DR) may involve T-helper or suppressor lymphocytes. With the availability of new genetic methodology, significant advances in our understanding of the inheritance pattern of some diseases have been made. Studies of the newly discovered HLA polymorphisms, such as the DQ and DP markers at the cellular level (Class-II genes products) and restriction sites at the DNA level are likely to lead to new associations. Further, the discovery of the monoclonal antibodies recognizing distinct epitopes on HLA class-II molecules and DNA probes recognizing DNA flanking sequences would help greatly in providing much stronger genetic marker systems in these diseases.

The uniqueness of an individual within a species is a fascinating phenomenon of nature. It is known that the success of a transplanted tissue is dependent on the extent of the genetic difference between the donor and the recipient. If a putative donor expresses a genetically controlled determinant that is absent in the recipient, the same is recognized as 'non-self' by the recipient's immune apparatus leading to graft rejection. These genetically controlled antigenic differences between individuals were first detected on red cells by Landsteiner[1] following his discovery of the blood groups in man matching for which had a major effect on the survival of a transplanted tumour. Subsequently, Gorer[2] on the basis of his transplantation experiments involving specific inbred strains of mice further extended the concept of blood group incompatibility to histo-(in)-compatibility. The antigens most relevant for transplantation were called 'Histocompatibility Antigens' by Snell[3] whose work showed that atleast in the mouse, as many as 20 loci governing histocompatibility on leucocytes existed. Out of these, one complex locus termed H-2 predominated in the sense that it controlled the 'strong' transplantation antigens which provoked intense allograft reactions that were most difficult to suppress. This H-2 locus was termed the 'Major Histocompatibility Complex' abbreviated as MHC which is now known to exist in almost all vertebrate species. The H-2 system of the mouse has in many respects been an important model for the study of the HLA system which is the MHC of man. In parti-

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cular, extensive research during the past nearly one decade has established the HLA-linked control of immune response to a variety of pathogens. Antigen presentation by macrophages, cell cooperation amongst various lymphoid subsets, the suppressor and the helper effects etc all seem to be governed by genes within the HLA complex. Today, HLA has emerged as one of the most important immunogenetic and histocompatibility systems in man coding for a huge multi-allelic family of cell membrane glycoproteins present on the surface of nucleated cells. Besides its prime role in transplantation and immunoregulatory mechanisms, HLA has proved to be a powerful diagnostic and/or prognostic tool in various diseases including understanding of their immunopathogenesis and causation.

Historical background

In man, the genetic polymorphism of the leucocyte antigens was first recognized by Dausset[4] who reported the existence of white cell agglutinins in the sera of polytransfused individuals. He named the first leucocyte isoantigen identified as 'MAC' (present equivalent, HLA-A2+A28). Subsequently, independent discoveries by van Rood[5] and Payne[6] revealed that pregnancy *per se* provided an effective stimulus for the formation of such leucocyte antibodies due to feto-maternal incompatibility. Later, with the introduction of improved statistical methods and computer technology[7], a detailed analysis of the reaction patterns in these sera was possible. van Rood thus defined the first two leucocyte antigens behaving as the products of allelic genes which he termed 'group four' (now termed Bw4 and Bw6). Soon, using the same statistical methods, a second set of antigens called 'LA' ('L' for leucocytes and 'A' for the first locus) was described.[8] As more antigens were discovered, it became clear that these fell into two series controlled by a set of alleles at two closely linked loci,[9,10] now termed as HLA-A and HLA-B. Thus the human MHC was born. Originally, it was termed HL-A but subsequently, the WHO-IUIS Terminology Committee[11] dropped the hyphen for simplicity since the system was envisaged to have many more linked loci. In the early 70's, a third closely linked locus, AJ, (now HLA-C) was defined serologically[12] located between HLA-A and-B.

Employing cellular typing techniques such as the mixed lymphocyte culture (MLC), a fourth set of HLA antigens or alleles was defined which was named HLA-D[13,14] situated outside the HLA-B locus. Recently, serological procedures were developed which recognized a set of alloantigens closely related to the HLA-D locus and named HLA-DR.[15,16] The pace for the growth and complexity of the HLA system was set by an exemplary international cooperation amongst scientists through nine histocompatibility workshops started first in 1964 by Amos. These workshops laid the foundation for the exchange of sera and reagents amongst a large number of participating laboratories, and the combined analysis of the resulting data has been responsible for many of the discoveries in the human MHC and their applications to biology and medicine.

MHC of Mouse and Man

A unique characteristic of the MHC is its extraordinary polymorphism which is closely related to its immense biological significance. The MHC consists of co-dominant genes at a series of closely linked loci, found on chromosome 17 in mouse and on short arm of chromosome 6 in man. The HLA in man is approximately 2 cM (centimorgan) in length[17] lying close to the loci coding for the red cell enzyme phosphoglucomutase-3[18] and glyoxylase.[19] Presently, atleast eight distinct loci have been defined and these code for three different classes of molecules. **Class I gene products** are membrane glycoproteins present on the cell membrane of almost all nucleated cells and are

coded for genes situated at the three loci viz HLA-A,-B and -C. The alleles in these loci are numbered numerically i. e. A1, B5 etc. and can be determined serologically by the comple ment dependent lymphocytotoxicity assay. The comparable class I molecules in the mouse H-2 are coded by K and D loci.

The class II gene products are structurally, biochemically and functionally different from the class I molecules. These antigens have a rather restricted tissue distribution, being expressed preferentially on B lymphocytes (but also on activated T lymphocytes) and macrophages. In man, these have been encoded by HLA-D locus which is considered homologue of the mouse H-2 I-region. The alleles in this locus were originally detected by the mixed lymphocyte culture (MLC) technique using homozygous typing cells (HTC) from donors of known D-locus types as standard stimulating cells. The class II gene products also include the recently defined D-related serological determinants (HLA-DR antigens) which correspond to the Ia (immune associated) antigens in the mouse. While the exact relationship between the D and DR remains obscure, it is plausible that both may be carried by the same molecule although they might be different determinants on this molecule.[20] More recently, a few other loci have been added to the class II gene products. Some of the alloantigenic specificities in these loci have been found to be strongly associated with two or more HLA-DR antigens. This has led to the identification of two more closely related systems; MB[21] and MT.[22] At present, there is a considerable debate as to whether MB and MT markers exist as epitopes on the same DR molecule or whether they are carried on Ia molecules distinct from DR. Another multi-allelic secondary B cell locus antigen system mapping centromerically to DR and named as 'SB' has been described.[23] The gene products of the SB locus are defined by a special primed lymphocyte typing (PLT) assay system and may have similar biological functions in vivo as the HLA-D/DR.

Genes coding for some components of the complement system are also coded in the MHC and comprise the **class III products**. Some of these serum complement factors are genetically polymorphic and mapping of their structural loci within the HLA complex makes them useful as additional genetic markers of this region. These include C2 and C4 of the classical complement pathway and Bf (properdin factor B) of the alternate pathway. The C2 system has one locus and 4 alleles : A (acidic), B (basic) C (common) and Q2 (null). C4 is comparatively more polymorphic with two loci containing 10 alleles each—C4A (Rodgers red cell antigen) and C4B (Chido red cell antigen) with null alleles frequent at each locus.[24] The Bf system has two common (F and S) and two less common electrophoretic variants (F1 and S1). In addition to the factors for the complement, 21-hydroxylase (21-OH) has also been mapped to the left of the HLA-B locus and nearer to the HLA-D/DR locus. Finally, although biochemically similar to class I products, a number of so called lymphocyte differentiation antigens are suggested to form a distinct class of antigens; **class IV products.**[25] These in the mouse are Qa and Tla. Their human equivalents are yet to be found. A schematic summary of the classes and loci of MHC genes of mouse and man is given in fig.1.

Some characteristics of HLA antigens

A. Polymorphism : HLA system is the most highly polymorphic genetic system thus far known in man. Table I shows the presently known HLA specificities in each of the five loci. i. e. 20 in the locus A, 40 in locus B, 8 in locus C and atleast 12 in locus D/DR. A 'W' prefix in the number indicates a workshop specificity which though recognized serologically has not yet obtained the optimal definition. The complexity of the HLA system is illus-

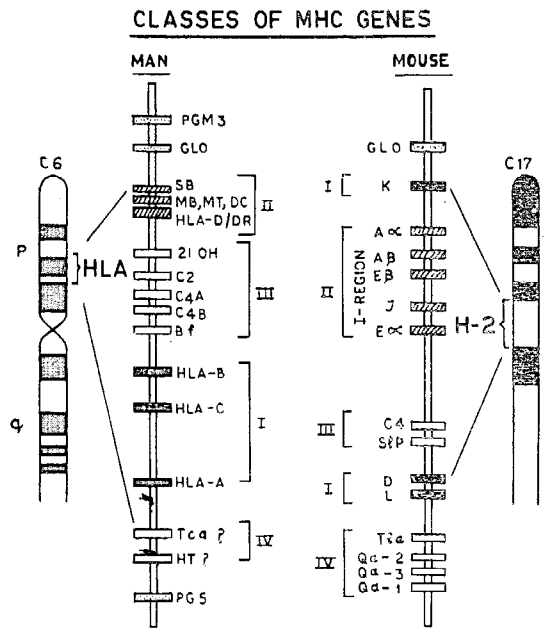

Fig. 1. A schematic respresentation of the classes and loci of MHC genes of mouse and man. The HLA in man is represented on a small region on the short arm of chromosome 6 and its homologue in the mouse, H-2 is located on chromosome 17. At least four classes of molecules (represented vertically) have been described in both species.

trated by a comparison with the ABO system. In the latter, there is only one locus with three alleles and six genotypes, whereas in the former, the class I and class II products alone comprise of more than five loci with nearly 100 codominant alleles and genotypical combinations already amounting to several million (approximately two thousand million or even more). If one adds to this complexity, the polymorphism of other genes in the HLA region coding for example, for factors C2, C4, Bf etc. the figure reaches so high that every human is expected to have a different gene combination. Such high polymorphism is indeed a necessity if one considers the role of the MHC in selfrecognition of various cells within a multicellular organism. In terms of donor selection for transplantation purposes, however, it means that individuals in a random population have a very little chance to be HLA identical.

Table I Complete listing of recognised HLA specificities.

HLA-A	HLA-B	HLA-C	HLA-D	HLA-DR
A1	B5	Cw1	Dw1	DR1
A2	B7	Cw2	Dw2	DR2
A3	B8	Cw3	Dw3	DR3
A23 (A9)	B12	Cw4	Dw4	DR4
A24 (A9)	B13	Cw5	Dw5	DR5
A25	B14	Cw6	Dw6	DRW6
A26 (A10)	B15	Cw7	Dw7	DR7
Aw 34	B16	Cw8	Dw8	DRw8
A11	B17		Dw9	DRw9
A28	B18		Dw10	DRw10
A29	B21		Dw11	DRw11
A30	B22		Dw12	DRw12
A31 (Aw19)	B27		Dw13	DRw13
A32	B35		Dw14	DRw14
Aw33	B37			
Aw36	B38 (Bw16)			
Aw43	B39 (Bw16)			
	B40			
	Bw41			
	Bw42			
	B44 (B12)			
	B45 (B12)			
	Bw46			
	Bw47			
	Bw48			
	B49 (w21)			
	Bw50 (w21)			
	B51 (B5)			
	Bw52 (B5)			
	Bw53 (B5)			
	Bw54 (Bw22)			
	Bw55 (Bw22)			
	Bw56 (Bw22)			
	Bw57 (B17)			
	Bw58 (B17)			
	Bw59			
	Bw60 (B40)			
	Bw61 (B40)			
	Bw62 (B15)			
	Bw63 (B15)			
	Bw4			
	Bw6			

Every individual being diploid inherits two antigens of each locus, one each from either parent. A set of antigens on the same chromosome inherited *en bloc* from one parent is called

a *haplotype*. The two HLA haplotypes in an individual derived after family testing constitute his *genotype* whereas the total HLA antigen profile is called *phenotype*. Fig. 2 illustrates the simple Mendelian segregation of HLA haplotypes from the parents to the offspring. Accordingly, a maximum of four different sets of children are possible in a family. Another child in this family, therefore, has a 25% chance to be HLA identical with one of his brothers/sisters, 50% chance to be haplo-identical (sharing one parental haplotype only) and 25% chance to be HLA non-identical i.e. total mismatch. While studying diseases for susceptibility governed through HLA-linked genes in families, one tries to ascertain the extent to which this random segregation figure of 1:2:1 deviates.

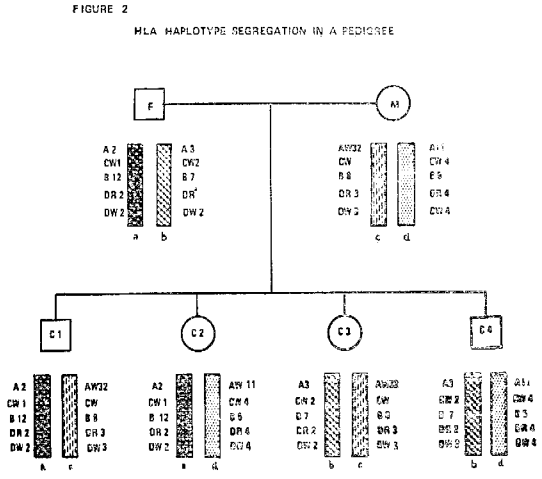

Fig. 2. HLA haplotype segregation in a family.

B. Linkage disequilibrium : A prominent genetic characteristic of the HLA system is that certain antigens are associated more frequently than would be expected on the basis of their individual gene frequencies. This phenomenon is called linkage disequilibrium and it is expressed as the delta ($\triangle$) value. Essentially, it is the difference between the observed haplotype frequency and the product of the respective gene frequencies.[26] For example, in White Caucasoids, the gene frequency of HLA-A1 is 0.17 and that of B8 is 0.11. Therefore, the expected frequency of A1, B8 to occur as haplotype is 0.17×0.11 i. e. 0.019. However, the observed frequency for both these alleles occuring together is 0.09. Incidently, A1, B8 are found to be in strong linkage disequilibrium along with DR3 in Caucasians. The delta values for different combinations of HLA alleles vary between populations. One of the explanations for this phenomenon is, that the genes are held in these biologically desirable combinations by natural selection. The knowledge of linkage disequilibrium between various alleles of the HLA loci is indeed important in disease association studies.

C. Cross reactivity : Another chracteristic feature of the HLA system is the serological cross reactivity between various antigens. Each HLA antigen is a multivalent cluster of possibly several antigenic determinants. Each of these clusters differ from others in their number and type of determinants. If two HLA antigens share enough common determinants, they may react with antisera of either specificity and thus appear cross reactive. The antigens within each locus show a larger amount of cross reactions, but there is little if any between the loci. Some of the prominent cross reactions between alleles of the HLA-A, -B, and -DR loci have been described.[27]

Biochemistry of the HLA Antigens

The class I molecules have two chains : a glycosylated heavy chain of 44,000 daltons binding non-covalently with a non-glycosylated light chain of 12,000 daltons (β2 micro-globulin)[28] The detailed structural organization of the two chains reveals that the heavy chain is anchored in the cell membrane and can be divided on the basis of its structure into three external domains, each of about 90 aminoacids;

a trans-membrane region of about 40 residues and one intra-cytoplasmic domain of 30 residues.[29] The first and the second external domains appear to be most variable and constitute the site of the antibody attachment and T cell recognition. The heavy chain, therefore, contributes to the HLA polymorphism. The third external domain is the most highly conserved among the different class I molecules and is associated with $\beta 2$ microglobulin(Fig. 3). Apart from three external domains, the vertical bar of the heavy chain is divided into the exons indicated as Roman numerals. There is a marked homology in the aminoacid sequence between human $\beta 2$ microglobulin and the HLA class I heavy chain and IgG.[30] There is thus reason to believe that HLA-A, -B, -C antigens and the immunoglobulin molecules may have an evolutionary common origin.

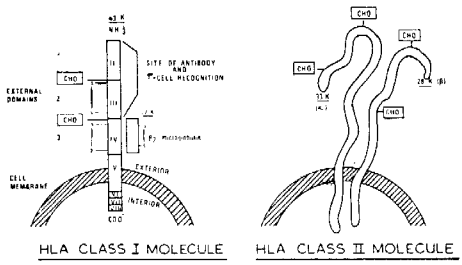

FIG. SCHEMATIC REPRESENTATION OF THE STRUCTURAL ORGANIZATION OF HLA CLASS I AND CLASS II MOLECULES.

Fig. 3. Schematic representation of the structural organization of HLA class I and II molecules. The former contains a heavy chain (43k) and a light chain (12k) with interchain disulphide bonds. The heavy chain is anchored in the cell membrane and contributes to the HLA polymorphism. The light chain is equivalent to the β_2-microglobulin which exists on chromosome 15. The class II molecules have an α (33k) and a β (28k) chain both of which pierce the cell membrane.

The HLA class II molecules similarly consist of two glycosylated polypeptide chains, each with a molecular weight of 33,000 (33k) and 28,000 (28k) daltons respectively. $\beta 2$-microglobulin is absent from these antigens. Only the 33k chain is coded by a gene within the HLA region and carries the polymorphic specificities detected by allogeneic antisera.

Role in Immune Response

The concept regarding the involvement of HLA in immune response is based on our knowledge on the H-2 system in mice since genetic heterogeneity of man could not be manipulated by inbreeding. Thus systematic experimental approach is denied in humans. The first indication that the MHC could play a key role in the regulation of the immune response came from studies in guinea pig and mouse by Benacerraf and McDevitt.[31] These investigators showed that immune response to synthetic polypeptides was controlled by immune response (Ir) genes. These Ir genes are linked to the MHC and map in the H2-I region which is equivalent to the HLA-D/DR region of man. At present, it has become clear that the major biological role of the MHC gene products is that they serve as 'recognition units' for lymphocytes, thus constituting a defence mechanism against non-self and altered self.[32] The concept that the T-cell activation depends not only on the recognition of the antigen but also on the simultaneous recognition of the MHC products has become widely accepted. This phenomenon has become known as *MHC restriction.* The full appreciation of the key role of the MHC in the cellular recognition of antigens came with the experiments of Zinkernagel and Doherty[33] who demonstrated that the killing of lymphocytic choriomeningitis virus (LCV) infected target cells occurred only when the cytotoxic effector cell and the target cell expressed the same H-2 haplotype.

To summarize, there appears to be a *bipolar* division of the functions of the products of the HLA complex. The class I products appear to serve as 'targets' when a cell is either infected by a virus or covered with a hapten. On the other hand, the class II gene products appear to serve as 'regulator' between the various cell

subgroups involved in the immune response. Thus functions of the antigen-presenting cells (macrophages, dendritic cells, endothelial cells, langerhans cells) bringing about cell interactions between T and B cells, T cells and macrophages, T and T cells are governed by the Ir genes coded within the class II determinants. If an antigen such as PPD is presented by human macrophages, the presence of atleast one DR identity is apparently necessary for the presentation to be effective and for lymphocytic proliferation to occur.[34] Such a restriction phenomenon is probably the most direct proof for the involvement of products of the HLA complex in regulation of the immune response of man. Indirect proof to this has come from several studies of HLA and diseases e.g. measles antibody in multiple sclerosis,[35] hepatitis B virus infection,[36] streptococcal antigens and HLA-B5,[37] influenza A virus and HLA-Bw16,[38] rubella virus vaccination and association with A28, B14 and Bw22,[39] vaccinia virus and HLA-Cw3[40] etc.

Recently, the self-recognition function of the MHC gene products has been suggested[41] which requires an identity of ubiquitous molecules of class I antigens at the surface of the interacting cells. Class II molecules are not apparently implicated in this phenomenon. Self recognition is important in biological context of generalized cell adhesions, homing, rosettes and contact inhibition, which are so very vital for the harmonious cohabitation and efficient coordinated functions of the body. The question that comes to mind is whether the MHC gene products are indispensable to the survival of the cells or organisms. For isolated cells *in vitro*, the answer is no, as shown by experiments on Daudi cell lines[42] in which though HLA genes are present, these are not expressed since the β2-microglobulin in this cell line lacks the requisite genes for coding. For complete organisms, the answer comes from a natural experiment discovered recently and entitled, 'bare lymphocyte syndrome'.[43] This involved a child suffering from severe combined immunodeficiency (SCID) in which the HLA class I molecules were not expressed on the surface of the lymphoid cells, though the class II antigens (HLA-DR) were detected. Thus even though life without HLA antigens is possible, it will be a precarious life in view of the resultant SCID.

HLA and disease associations

Ever since the demonstration by Frank Lilly[44] of a strong association between H-2 and gross virus leukemogenesis in inbred mice and of Amiel[45] reporting an association between HLA antigen '4C' (now recognized as B5, BW35, B15 and B18) and Hodgkins lymphoma in humans, the usefulness of HLA studies in clarifying the genetics of various diseases has been substantiated. Also, our knowledge of the biological function of the HLA gene products and of the homologous MHC's in other species has increased considerably although there are still a lot of un-answered questions. In particular, consensus regarding the exact mechanisms underlying HLA-controlled susceptibility to various diseases is yet to be reached.

General considerations : When looking for a possible relationship between HLA and a disease, two different approaches can be used. One of these consists of population studies in which the gene frequencies of HLA antigens in a group of unrelated patients are compared with the corresponding frequencies in a group of healthy controls. This approach gives information only on the *association* which could either be due to direct causation (that is the associated antigen itself is responsible for the higher or lower susceptibility) or linkage disequilibrium of a disease susceptibility gene (DS gene) with the associated HLA marker. Population studies, in general, are much easier to perform but have a number of pitfalls relating to designing of the protocol, ethnicity of the population, statistical considerations etc. The data must

be compared with normal healthy group representing the same ethnic background since HLA antigen frequencies are known to vary significantly from population to population and between various ethnic groups of the same population. The other approach involves the family studies which allows us to see if affected relatives share HLA haplotypes more often than expected according to the general genetic rules. Family studies have a number of advantages : (i) they allow us to detect '*genetic linkage*' between the HLA locus or allele and a major disease-predisposing gene: (ii) there are no problems associated with population heterogeneity: and (iii) those with frequent linkage disequilibria. However, in practical terms, it is more difficult to collect the appropriate families for study fulfilling all the criteria.

Current perspective : A number of review articles have been written on the subject of HLA and disease associations which are quite informative.[46-50] Most of the data has been compiled in the HLA and disease registry of Copenhagen.[51] Some of the conditions which are believed to be associated and/or linked to the HLA system at the present time are given in table II. A comparison of the data in this table with that reported a few years ago suggests that whereas the association of some diseases with a particular HLA allele has been confirmed in other major populations of the world e. g. B27 with ankylosing spondylitis and other related spondyloarthropathies, a few diseases showing doubtful or no association previously have now been found to be definitely associated e.g. DR4 with rheumatoid arthritis and DR3 with systemic lupus erythematosus etc.

Autoimmune diseases : With the feasibility of the serological typing of the DR determinants, a major advance seems to have taken place in diseases with autoimmune character since many of them known previously to be HLA-B associated have now shown much stronger associations with HLA-D/DR antigens, thus implicating the role of Ir genes in governing their susceptibility. The best known examples in this category have been insulin-dependent diabetes mellitus (IDDM), multiple sclerosis, Grave's disease, Addisons' disease, myasthenia gravis and perhaps rheumatic heart disease. Data from the Western Caucasoid populations indicates that these diseases show a much stronger association with HLA-DR3 than with B8 or B15. In IDDM, however, the B-allele has been reported to be variable in different populations, being Bw54 in the Japanese[52] and Bw21 (W49) in the north Indians.[53] In some of these diseases, typing of the class-III complement components has been particularly useful in identifying the whole haplotype of linked genes conferring suscepti bility and/or resistance. The best examples have been IDDM and RA. Linkage studies in multiple case IDDM families living in the Paris area have identified three 'high risk' haplotypes or segments of them—A2, CW3, B15, BfS, DR4; AW30, CW5, B18, BfF1, DR3 and A1, B8, BfS, DR3.[54] Our recent data in the IDDM patients of north Indian origin revealed the 'high risk' IDDM haplotype to be A28, Bw21, BfS1, DR3[55]. Curiously, the 'low risk' haplotype conferring resistance or protection in this disease has been found to be common in all populations viz A3, B7, DR2. Such data could be useful in understanding the model of inheritance of IDDM and other diseases in varius populations. Recently, with the demonstration of a rare C4B allele, Dawkins and coworkers[56,57] have successfully identified a 'supratype' with alleles at multiple loci between HLA-B and DR to be associated with RA. This supratype which occurs in approximately 10% of patients with RA but only approximately 1% of the population as a whole has been characterized by HLA-Bw62, CW3, BfS, C4B2.9, DR4. Interestingly, the same supratype is also associated with IDDM suggesting some relationship between this disease and RA. Indeed, evidence has accumu-

Table II. Prominent associations between HLA and diseases.

	HLA	Frequency (%)		Relative risk
	Antigen	Patients	Controls	
1. Rheumatic				
Ankylosing spondylitis	B27	92	5	193
Reiter's disease	B27	80	5	66
Acute anterior uveitis	B27	55	5	20
Rheumatoid arthritis	DR4	64	12	14.7
Juvenile R. A.				
—Pauciarticular	DR5	50	16.2	5.2
—All cases	DRW8	23	7.5	3.6
2. Endocrine				
Insulin dependent diabetes	B8	—	—	2.4
	B21	35	4	12
	DR3(Ind.)	80		
	DR3(West)	56	28	3.3
	DR4	75	32	6.4
	DR2	12	44	0.2
Grave's disease	DR3	56	26	3.7
Idiopathic addison's disease	DR3	69	26	6.3
SLE	DR3	70	28	5.8
Celiac disease	DR3	79	26	10.8
3. Neurologic				
Myasthenia gravis	BW21	19	4	5.0
	B8	24	12	2.4
Multiple sclerosis	DR2	59	26	4.1
4. Heterogenous group				
Hodgkins disease	A1	40	32	1.4
Idiopathic hemochromatosis	A3	76	28	8.2
	B14	16	4	4.7
Optic neuritis	DR2	46	26	2.4
C2 deficiency	DR2	—	—	—
Psoriasis vulgaris	CW6	87	33	13.3
Dermatitis herpetiformis	DR3	85	26	15.4
Membranous nephropathy	DR3	75	20	12.0
Pernicious anemia	DR5	25	6	5.4
5. Infectious diseases				
Leprosy				
—Tuberculoid (TT)	DR2	Family data		
	DRW6			
—Lepromatous (LL)	MT1	All populations		
Pulmonary tuberculosis	DR2	Family data		
	DRW6			

The above data is based on reports from the HLA and disease registry of Copenhagen[54], and from our own in the population of North India published for various diseases (See reference in this paper and in Mehra and Malaviya[19]).

lated suggesting that these two diseases do cluster within families.[57] It will be interesting to see if there are other supratypes involved in RA and IDDM or for that matter, in other autoimmune disorders. It will also help in clarifying whether the association with D/DR antigens are the primary ("Causative") ones or secondary i.e. due to linkage disequilibrium with other HLA factors.

Rheumatological disorders : The discovery of the remarkable association between ankylosing spondylitis (AS) and B27 (nearly 93% frequency of B27 in AS patients compared to 5—10% in controls; relative risk of approximately 192 times) has provided the researchers with an excellent model for studying the relationship between a disease process and an inherited antigen.[58] Apart from the Caucasoids, it has been observed in almost all populations viz. Japanese[59], American Blacks[60], Asian Indians etc. [61],[62] A similar increase in the frequency of B27 is seen in patients suffering from related spondylo-arthropathies[63] and in AS associated with two other chronic rheumatic disorders viz acute anterior uveitis (AAU) and Reier's syndrome (RS).[58],[64] In the Indian patients, whereas the presence of A9 (AW24) in combination with B27 confers greater susceptibility to AAU[65], antigen Bw35 affords protection in RS.[66] It appears therefore, that while B27 might be the primary gene conferring susceptibility in AS and related spondyloarthropathies, other HLA linked factors at the same or distant locus might influence the course and severity of the future spondylitic disease. The data at present indicates that whereas A2, B27 supratype confers greater susceptibility to AS and 'unclassifiable arthritis', the existence of A9 in B27 positive AS patient signifies the presence of AAU. A model of HLA-controlled susceptibility to spondylitic disorders is represented in fig. 4. Ultimately, a clinician may be able to design appropriate treatment in a patient based on his initial HLA phenotypic expression and early manifestation of symptoms.

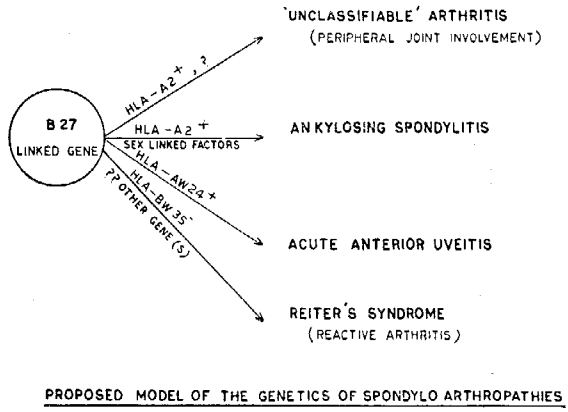

Fig. 4. A proposed model of the genetics of spondylo-arthropathies.

In rheumatoid arthritis, a chronic disorder clinically distinct from ankylosing spondylitis, there is no association with B27, but with Dw4/DR4 in Caucasoids,[67] Japanese[68] and Asian Indians.[69]

Infectious diseases : One of the most fascinating recent developments in HLA and disease association has been that concerning the infectious diseases. For example, in leprosy, following population studies by as many as 15 groups of investigators including two from our own group,[70],[71] as many as seven studies involving multi-sib families have been undertaken in four different popultion groups viz. Surinam[72] India[73],[74] Venezuela[75] and China (deVries 1984, personal communication). These studies have demonstrated an HLA encoded control of predisposition to not only polar tuberculoid but also lepromatous leprosy. In both cases, the observed segregation of HLA haplotypes in the healthy sibs in these families was random indicating that susceptibility to leprosy *per se* may not be controlled by HLA-linked genes. Also, whereas the Surinam as well as the Indian data pointed towards the recessive mode of inheritence, the Venezuela data indicates the dominant mode, thus suggesting the race specificity of the disease and HLA associated

factors. Recently, the data compiled at the Second Asian and Oceanian Histocompatibility Workshop revealed that polar lepromatous leprosy in most populations may be associated with a supertypic DR specificity, MTI.[76]

The situation as regards pulmonary tuberculosis (PTB) is indeed similar to leprosy. We are the first ones to report, that susceptibility to PTB may be controlled by HLA-linked genes and in linkage disequilibrium with HLA-DR2.[77] Again, a dominant mode of inheritence was observed in multi-sib families. The data on random sporadic PTB patients revealed the involvement of two genes in the DR locus governing susceptibility to this disease viz DR2 conferring susceptibility and DRW6 resistance.[78]

Neurologic disorders : HLA association studies have been extremely helpful in understanding the immunopathogenesis of neurologic disorders particularly those with an unknown aetiology. In myasthenia gravis, the association of B8 in Caucasian female patients is well established[79]. In Asian Indians, the disease is associated with Bw21 and Bw35[80] and the B8 reported in Caucasians is mainly confined to the young females with thymic hyperplasia, suggesting a possible heterogeneity in the disease. In multiple sclerosis, where both population as well as family studies have been performed, an association with A3, B7 has been noted by many investigators and is even stronger with DR2.[81]

Mechanisms : Several hypotheses have been put forward to explain mechanisms underlying disease associations : (i) The associations found may in fact be due to *chance* alone because of the stratification of populations, a particular HLA specificity gets precipitated giving rise to increased frequency of this allele in a disease process. Though, this may sound possible theoretically, it appears to be a remote possibility in view of the extreme degree of HLA polymorphism. (ii) HLA antigens may function as or *interfere with cell surface receptors* for particular pathogens. Although this type of mechanism appears to account for the Duffy red cell antigens,[82] there is currently no evidence to show that HLA antigens function in this manner. (iii) Sharing of antigenic determinants between histocompatibility antigens and pathogenic microbes, rendering the host unable to react immunologically against the pathogen, a phenomenon referred to as *'molecular mimicry'*. Evidence has been presented in favour of this form of cross reactivity between B27 and *Klebsiella* species leading to the development of ankylosing spondylitis.[83] (iv) Genes controlling the HLA antigens may be linked to *Ir genes* governing susceptibility or resistance to pathogenic microbes. This approach appears to account for most of the HLA and disease associations, in particular those involving D/DR antigens.

HLA and kidney transplantation

Independent observations by several transplant centres indicate that kidneys transplanted from HLA identical ('full house' matched) and ABO blood group compatible siblings function better and longer than those exchanged between unrelated and 'unmatched' donors. These combinations in general have a 5-year graft survival of around 85-90 per cent. In parent-to-child transplants or those involving a 50% matched sibling (one haplotype match), the figure is still encouraging to a 60=65% after 5 years. The survival figures involving well matched cadaver donors in good centres are almost equal to those of the parent-child combinations. A 5-year follow-up data on more than 5,000 first cadaver renal transplants performed in Eurotransplant suggests that grafts with no HLA-A or-B mismatches do ever 20% better than those mismatched for 3 or 4 antigens in these two loci.[84] With the introduction of DR matching in cadaver donor transplantation since 1977, a significantly better graft survival is seen in recipients who received a DR compatible

kidney than in those receiving kidney from a DR incompatible donor.[85] The data from most centres suggest that (a) even matching for one HLA-DR over and above the HLA-A and -B, antigen matching enhances the graft survival to more than 90% at 2-year post-transplant period[84] and (b) matching for both DR antigens without HLA-A, -B matching appears to result in good graft survival as well.

Presently, however, apart from the influence of HLA matching, the role of other factors such as pretransplant blood transfusions, positive or a negative cross match, presence of 'warm and cold' antibodies in the recipient's serum, age and sex of the donor etc are being investigated critically for their effect on overall graft survival. While there is no consensus reached as yet as to the number of pretransplant blood transfusions, their time duration before the actual transplant, the type of the blood used i.e. fresh, leucocyte poor or leucocyte free) etc, it is generally accepted as a major factor influencing graft prognosis. The details on all these factors are discussed by others in review articles on transplantation.[81-86]

HLA and paternity testing

The extreme degree of genetic polymorphism in HLA provides a highly discriminatory system yet defined in paternity testing. In the western world, HLA is the test of choice in cases of paternity disputes since no other system is as informative as HLA alone. If a child possesses an HLA gene not present in either parent, or if he lacks a factor that the putative father must pass on, then non-paternity is likely. Recently, an extraordinary case of disputed parentage twins and superfecundation was detected by HLA typing in which the twins were fathered by two different men.[87] A general data from most forensic laboratories in the world suggests that the probability of exclusions of a falsely accused father or evidence to support the paternity of a truely accused man using HLA alone can be calculated to be around 92.4%.[88] On the other hand, only after using 57 immunologic and biochemical genetic systems, the probability of excluding a falsely accused man chosen at random was calculated to be 98.8% for Blacks, 99.42% for Caucasians and 95.4% for the Japanese. From a practical point of view, few single laboratories possess the ability to test for most of those marker system and excluding HLA, no one single system is highly informative so that a small set of markers would not be very satisfactory collectively. This does not mean that HLA test can be used to prove paternity absolutely. However, the test report supported by the knowledge of the general prevalence of HLA antigens in a community can help draw reasonable conclusions. Also, if the HLA test results are combined with those of the common tests in the blood bank (blood groups ABO, MNS, Kell, Duffy, Kidd, P etc), the probability rises to nearly 98.5%.

Conclusions

The recent upsurge of knowledge concerning the vast complexity and biological significance of the genes and products of the major histocompatibility complex including the discovery of the Ir genes has helped the physician and the basic researcher in many ways. With regard to transplantation, apart from HLA matching, the beneficial effects of preoperative blood transfusions bringing about specific immune tolerance in the recipient have already paved the way for better graft prognosis. Thus, a more detailed analysis of the allogeneic response can now be made and applied to the definition of a better histocompatibility for kidney and bone marrow transplantation. The discovery of the association of a nubmer of diseases with HLA is even more promising and with an almost 'disease-a-month phenomenon' continuing, the validity of such reports to clinicians is beginning to be realized. Firstly, the associations thus far reported have contributed to the proper understanding of the aetiopathogenesis

and prognosis of several diverse and hitherto complex disease entities. Secondly, they have helped in de-differentiating a number of disorders and suggested a common pathogenetic link between them. The knowledge has thus provided the physician with a system of rational classification of many complex disorders and helped in understanding the heterogeneity in most of them. HLA typing can also contribute to the genetic counselling and in identifying an individual at risk to a particular disease. With the availability of DNA recombinant technology, it may henceforth be possible to know exact DNA sequence in the vicinity of the HLA genes which will serve as markers for discerning anomalies of susceptibility genes. Finally, the discovery of the functions of the MHC in self-recognition mechanism can help in our understanding of the differentiation and organization of cells in an organism for bringing about a coordinated function. In his Noble lecture, Prof. Dausset[89] observed, "the way already trod is but a simple introduction. There are still many marvelous pages to be written."

References

1. Landsteiner K : Individual differences in human blood, (Noble lecture) Science, 1931; 7 3: 403=409.
2. Gorer PA : The genetic and antigenic basis of tumor transplantation, J Path Bacteriol, 1937; 44 : 691-697.
3. Snell GD : Methods for the study of histocompatibility genes, J Genet, 1948; 49 : 87-108.
4. Dausset J : Leuco-agglutinins. IV. Leuco-agglutinins and blood transfusion, Vox Sang, 1954; 6 : 190-198.
5. van Rood JJ, Ernisse JG and van Leeuwen A : Leucocyte antibodies in sera from pregnant women, Nature, 1958; 181 : 1735-1736.
6. Payne R and Rolfs MR : Fetomaternal leukocyte incompatibility, J Clin Invest, 1958; 37, 1756-1763.
7. van Rood JJ : Leukocyte grouping, Thesis, University of Leiden, 1962.
8. Payne R, Tripp M, Weigle J et al : A new leukocyte isoantigen system in man, Cold Spring Harbor Symp Quant Biol, 1964; 29 : 285-295.
9. Ceppellini R, Curtoni E S, Mattiuz PL et al : Genetics of leucocyte antigens; a family study of segregation and linkage. Histocompatibility Testing 1967, Editors, Curtoni ES, Mattiuz PL, Tosi RM, Munksgaard, Copenhagen, 1967; p 149-187.
10. Kissmeyer-Nielsen F, Svejgaard A, Ahrons S et al : Crossing-over within the HL-A system, Nature, 1969; 224 : 75-76.
11. WHO-IUIS terminology Committee for factors of the HLA system. Histocompatibility Testing, 1975, Editors, Kissmayer-Nielsen F, Munksgaard, Copenhagen, 1975; p 5-11.
12. Sandberg L, Thorsby E, Kissmeyer-Nielsen F et al : Evidence for a third sub-locus within the HL-A chromosomal region. Histocompatibility Testing, 1970; editors Terasaki : Munksgaard, Copenhagen, 1970; p 165-169.
13. Thorsby E and Piazza A : Joint Report from the sixth International Histocompatibility Workshop Conference-II. Typing for HLA-D (LD-I or MLC) determinants. Histocompatibility testing 1975, Editor Kissmeyer-Nielsen F. Munksgaard, Copenhagen, 1975; p 414.
14. Keuning JJ : Typing for HLA-D, Thesis; University of Leiden 1978.
15. van Leeuwen A, Winchester R and van Rood JJ : Serotyping for MLC. II. Technical aspects, Ann NY Acad Sci, 1975; 254 : 289-295.
16. Bodmer WF : Ia Serology (Joint Report). Histocompatibility Testing 1977, Editors Bodmer WF et al, Munksgaard, Copenhagen, 1977; p 35-84.
17. Breuning MH, van den Berg-Loonen EM, Bernini LF et al : Localisation of HLA on the short arm 'of chromosome 6, Hum Genet, 1977; 37 : 131-139.
18. Lamm LU, Svejgaard A, Kissmeyer-Nielsen F : PGM : HLA is another linkage in man3 Nature (New Biology), 1971; 231 : 109-111.
19. Meera Khan P and Doppert BA : Rapid detection of GLO on cellulose acetate gel and the distribution of GLO variants in a Dutch population, Human Genet, 1976; 34 : 53-56.
20. Schreuder GM Th, Van Leeuwen A, Termijtelen A et al : Cell membrance polymorphisms coded for the HLA-D/DR region. I. Relation between D and DR, Human Immunol, 1982; 4 : 301-312.
21. Duquesnoy, RJ, Marrari M and Annen K : Identification of an HLA-DR associated system of B-cell alloantigens, Transplant Proc, 1979; 11 : 1757-1761.
22. Park MS Terasaki PI, Nakata S et al : MTI, MT2 and MT3-alternate allelic candidates for DRW

supratypic antigens, In : Terasaki PI. Histocompatibility Testing, 1980, p 858, Editor UCLA Tissue Typing Laboratory Press, 1980.

23. Shaw S, Johnson AH, and Shearer GM : Evidence for a new segreant series of B cell antigens that are encoded in the HLA-D region and that stimulate secondary allogenic proliferative and cytotoxic responses, J Exp Med, 1980; 152 : 565-580.
24. O' Neill GJ, Soo Young Jang, Tegoli J et al : Chido and Rodgers blood groups and distinct antigenic components of human complement C4, Nature, 1978; 273 : 668-670.
25. Snell DG : Studies in histocompatibility, Science, 1981; 213 : 172-178.
26. Bodmer WF, Bodmer J, Adler S et al : Genetics of '4' and 'LA' human leukocyte groups, Ann NY Acad Sci, 1966; 129 : 473-489.
27. Joysey VC and Wolf E : HLA-A-B and-C antigens, their serology and cross reaction, Brit Med Bull, 1978; 34 : 217-222.
28. Barnstable CJ, Jones EA and Crumpton MJ : Isolation, structure, and genetics of HLA-A, -B, -C and -DRw antigens, Brit Med Bull, 1978; 34 : 241-246.
29. Goodeno RS, Stroynowski I, McMillan M et al: Expression of complete transplantation antigens by mammalian cells transformed with truncted class I genes, Nature, 1983; 301 : 388-394.
30. Orr HT, Lancet D, Robb RJ et al : The heavy chain of human histocompatibility antigen HLA-B7 contains an immunoglobulin-like region, Nature, 1979; 232 : 266.
31. Banacerraf B and Mc Devitt HO : The histocompatibility linked immune response genes, Science, 1972; 175 : 273-279.
32. van Rood JJ, deVries RRP and Bradley BA : Genetics and biology of the HLA system, In : The Role of the Major Histocompatibility Complex in Immunobiology, Editor Dorf ME : Garland Press, New-York, 1981; p 59-114.
33. Zinkernagel RM and Doherty PC : Restriction o in vitro T cell mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system, Nature, 1974; 248 : 701-702.
34. Hirschberg H, Bergh OJ and Thorsby E : Clonal distribution of HLA restricted antigen reactive T cells in man, J Exp Med, 1979; 150 : 1271-1276.
35. Jersild C, Amritzboll T, Clausen J et al : Association between HLA antigens and measles antibody in multiple sclerosis, Lancet, 1973; I : 151-152.
36. Hills WD, Huis AH, Bias NB et al : Association of hepatitis B surface antigenaemia with HL-A locus B specificities, N Eng J Med, 1977; 296 : 1310-1314.
37. Greenberg LJ, Gray ED and Yunis EJ : Association of HL-A5 and immune responsiveness in vitro to streptococcal antigens, J Exp Med, 1975; 141 : 935-943.
38. Spencer MJ, Cherry JD and Terasaki PI : HLA antigens and antibody response after Influenza A vaccination, N Eng J Med, 1976; 294 : 13-16.
39. Spencer MJ, Cherry JD, Powell KR et al : Antibody responses following rubella immunization analysed by HLA and ABO types, Immuogenetics, 1977; 4 : 365-372.
40. deVries RRP, Kreeftenberg HG, Loggen HG et al : In vitro immune responsiveness to Vaccinia virus and HLA, New Eng J Med, 1977; 297 : 692.
41. Dausset J and Contu L : Is the MHC a general self recognition system playing a major unifying role in an organism, Hum Immunol, 1980; 1 : 5-17.
42. Fellous M, Kamoun M, Dausset J et al : Induction, of HLA expression in Daudi cell by cell fusion Immunogenetics, 1977; 5 : 423.
43. Touraine JL : The bare lymphocyte syndrome, report on the registry, Lancet, 1981; Z1 : 319-321.
44. Lilly F, Boyse EA and Old LJ : Genetic basis of susceptibility to viral leukemogenesis, Lancet, 1964; 2 : 1207-1209.
45. Amiel JL : IN : Histocompatibility Testing, Editors : Curtoni ES, Mattiuz PL and Tosi RM : 1967; p 79-81. (Report of a conference and workshop, Torino and Saint—Vincent, 14-24 June, 1967), Copenhagen, Munksgaard.
46. Ritzman SE : HLA patterns and disease associations, JAMA, 1976; 236 : 2305-2309.
47. Bodmer WF : The HLA system, Brit Med Bull, Scientific Editor, 1978; Vol 34.
48. Mehra NK : HLA—an overview, Ind J Ped, 1982; 49 : 863-872.
49. Mehra NK and Malaviya AN : The HLA system and its applications in clinical medicine, J Assoc Phy India, 1983; 31 : 167-172.
50. Svejgaard A, Platz P and Ryder LP : HLA and Disease, 1982. A survey, Immunological Rev, 1983; 70 : 193-218.
51. Svejgaard A, Morling N, Platz P et al : HLA and diseases, in : Immunology 80. Progress in Immunology IV, Editors Fougereau M and Dausset J : Academic Press, London, 1980; p 530-540.

52. Kawa A, Makazawa M, Sekiguchi S et al : HLA system in Japanese patients with diabetes mellitus, Diabetes, 1977; 26 : 591.

53. Mehra NK, Vaidya M C and Ahuja MMS : Diabetes Mellitus : In : Proceedings Second Asia and Oceanian Histocompatibility Workshop Conference, Melbourne, 1981.

54. Contou L, Deschamps I, Lestradet H et al : HLA haplotype study of 53 juvenile insulin dependent diabetic (I.D.D.) families, Tissue Antigens, 1982; 20 : 123-140.

55. Mehra NK, Bhatia E, Ahuja MMS et al : Possible HLA supratypes governing susceptibility to insulin dependent diabetes mellitus in North India, (In preparation), 1984.

56. Kay PH, McCluskey J, Christiansen FT et al : Complement allotyping reveals new genetic marking in rheumatoid arthritis and diabetes millitus, Tissue Antigen, 1983; 21 : 159:160.

57. Dawkins RL, Christiansen FT, Kayph et al : Disease associations with complotypes, supratypes and haplotypes. Immunol Rev. 1983; 70 : 5-22.

58. Brewerton DA, Caffrey M, Hart FD et al : Ankylosing spondylitis and HL-A27, Lancet, 1973; i : 904-907.

59. Sonozaki H, Seki H, Chang S et al : Human lymphocyte antigen, HL-A27 in Japanese patients with ankylosing spondylitis, Tissue Antigens, 1975; 5 : 131-136.

60. Khan MA, Braun WE and Kushner I : Low frequency of HLA-B27 in American Blacks with ankylosing spondylitis, Clin Res, 1976; 24 : 331.

61. Malaviya A, Mehra NK, Adhar GC, et al. : The clinical spectrum of B27 related rheumatic diseases in India; J Assoc Phy Ind; 1979; 27:487-492.

62. Mehra NK, Vaidya MC, Bhat RC et al : Histocompatibility antigens in seronegative spondarthritides syndrome; Aspects Allergy and Applied Immunology, 1979; 12:151-154.

63. Mehra NK, Prakash S, Vaidya MC et al : Ankylosing spondylitis, Reiter's disease and other HLA-B27 related spondyloarthropathies in North India, in : Immunogenetics in Rheumatology, Editor Dawkins R L, Excerpta Medica Holland, 1982; p 185-187.

64. Khan MA, Kushner I and Braun WE : Association of HLA-A2 with uveitis in HLA-B27 positive patients with ankylosing spondylitis, J Rheumatol, 1981; 8:295-298.

65. Mehra NK, Khan MA, Vaidya MC et al : HLA antigens in acute anterior uveitis and spondyloarthropathies in Asian Indians and their comparison with American Whites and Blacks, J Rheumatol, 1983; 10:981-984.

66. Mehra NK, Taneja V and Malaviya AN: Evidence to show MHC linked factors other than HLA-B27 governing susceptibility to spondyloarthropathies in Asian Indians, Tissue Antigens, 1984, (in press).

67. Stastny PN : Association of B-cell alloantigen DRw4 with rheumatoid arthritis, New Eng J Med, 1978; 298:869-871.

68. Nakai Y, Wakisaha A, Aizawa M et al : HLA and rheumatoid arthritis in the Japanese, Arthritis and Rheumatism, 1981; 24:722-725.

69. Mehra NK, Vaidya MC, Taneja V et al : HLA-DR antigens in rheumatoid arthritis in North India, Tissue Antigens, 1982; 20:300-302.

70. Dasgupta A, Mehra NK, Ghei SK et al : Histocompatibility antigens (HLA) in leprosy, Tissue Antigens, 1975; 5:85-87.

71. Mehra NK, Dasgupta A, Ghei SK et al : HLA antigens and leprosy, Microbiol letters, 1976; 3:79-83.

72. deVries RRP, Lai A, Fat RFM et al : HLA linked genetic control of host response to **Mycobacterium leprae,** Lancet, 1976; 2:1328-1330.

73. deVries RRP, Mehra NK, Vaidya MC et al : HLA linked control of susceptibility to leprosy, Tissue Antigens, 1980; 16:294-304.

74. van Eden W, deVries RRP, Mehra NK et al : HLA segregation of tuberculoid leprosy: confirmation of the DR2 marker, J Infect Dis, 1980; 141:693-701.

75. van Eden W, and deVries RRP et al HLA and leprosy : an evaluation Lep Rev. 1984; 55:89-104.

76. Serjeantson SW, Vaidya MC, Chan SH et al : Leprosy : Proceedings second Asian and Oceanian Histocompatibility Workshop Conference, Editors Simons MJ and Tait BD : Immunopublishing, Victoria, Australia, 1983; p 379-401.

77. Singh SPN, Mehra NK, Dingley HB et al : HLA linked control of susceptibility of pulmonary tuberculosis and association with HLA-DR type, J Infect Diseases, 1983; 143:676-681.

78. Singh SPN, Mehra NK, Pande JN et al : HLA-A, -B,-C and -DR antigen distribution in pulmonary tuberculosis in North India, Tissue Antigens, 1983; 21:300:304.

79. Behan PO : Immune disease and asociations with myasthenia gravis, J Neurol Neurosurg Psychiat, 1980; 43:611-621.

80. Mehra NK, Ahuja GK, Taneja V et al : HLA antigens and myasthenia gravis in North India, J Neurol Neurosurg Psychiat, 1983; 46:361-363.

81. Batchelor JA, Compston A and McDonald WI : HLA and multiple sclerosis, Brit Med Bull, 1978; 34:279-284.

82. Miller LH, Mason SJ, Clyde DF et al : The resistance factor to **Plasmodium vivax** in blacks : the Duffy blood group genotype FyFy, N Eng J Med, 1976; 295:302-304.

83. Ebringer A, Cowling P, Nawa-Suh, N et al : In HLA and Disease : predisposition to disease and clinical implications (Abstract) Vol 58, p 27 (1976). (ed) Institute National de la Sante et de la Recherche Medicale, Inserm, Paris.

84. van Rood JJ, Persijn GG, Cohen B et al : Hierarchy of factors which influence kidney graftsurvival, in : Transplantaion and Clinical Immunology Vol, III, Editors Touraine JL et al, Excerpta Medica, Amsterdam, 1981, p 147.

85. Morris P J and Ting A : Studies of HLA-DR with relevance to renal transplantation, Immunol Rev, 1982; 66:103-131.

86. Santiazo-Delpin EA : Immunobiology of organ transplantation, in : Immunobiology of Transplantation, Cancer and Pregnancy, Editor, Ray PK, Pergamon Press, N Y, 1983; p 88-110.

87. Terasaki PI, Gjertson D, Bernoco D et al : Twins with two different fathers identified by HLA, N Eng J Med, 1978; 299:590-592.

88. Schacter BA, Hsu SH and Bias WB : HLA and other genetic markers in disputed paternity. A report of 50 cases, Transplant Proc, 1977; 9:233-239

89. Dausset J : The Major Histocompatibility Complex in man. Science, 1981; 23: 1469-1474.