HISTOCOMPATIBILITY SYSTEM (HLA) & INFECTIONS

ESSAY

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BY

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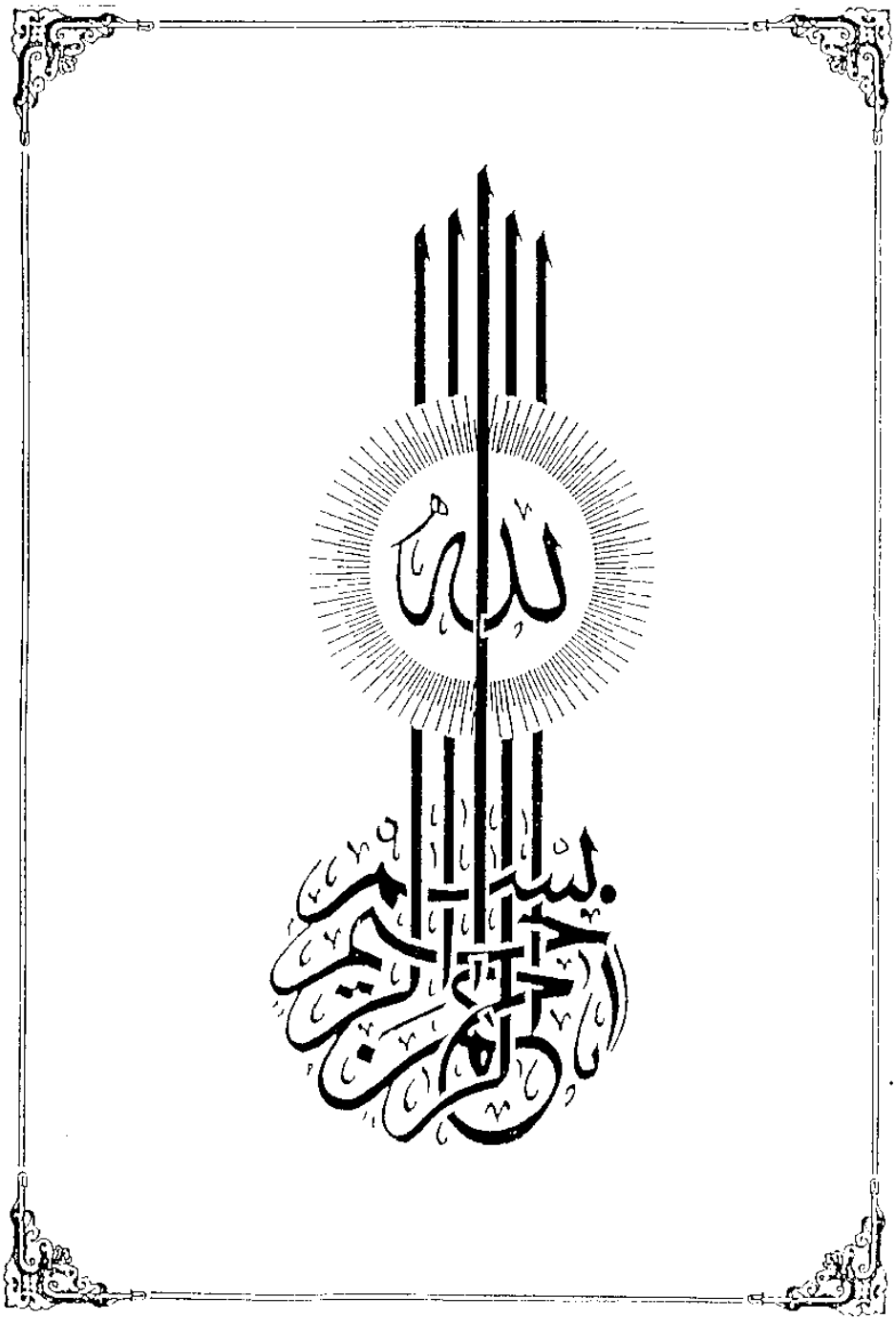
Dedicated To

My Husband, Daughter and Parents

With All Affection And Respect



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CONTENTS

CONTENTS

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◊◊◊O◊◊◊
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AIM OF THE WORK

The discovery of associations between certain diseases and HLA system represents one of the most important advances in clinical medicines of the last decade and provides for the first time, a firm foundation for understanding the aetiology and pathogenesis of many diseases.

This work comprises the study of relation between HLA system and many infectious diseases. These diseases may be bacterial diseases or viral diseases. HLA may be associated with the susceptibility and/or resistance to an infectious disease. It may also has a relation to the severity of the course of the disease we try to explain examples of these diseases-HLA relation in this work.

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Review of Literature

The HLA System:-

The HLA complex (Human leucocyte antigen, or Histocompatibility loci antigen complex), is a multigene family on the short arm of human chromosome number 6, that encodes molecules critical to self non self discrimination (Fig. 1) (Pollack and Rich, 1985).

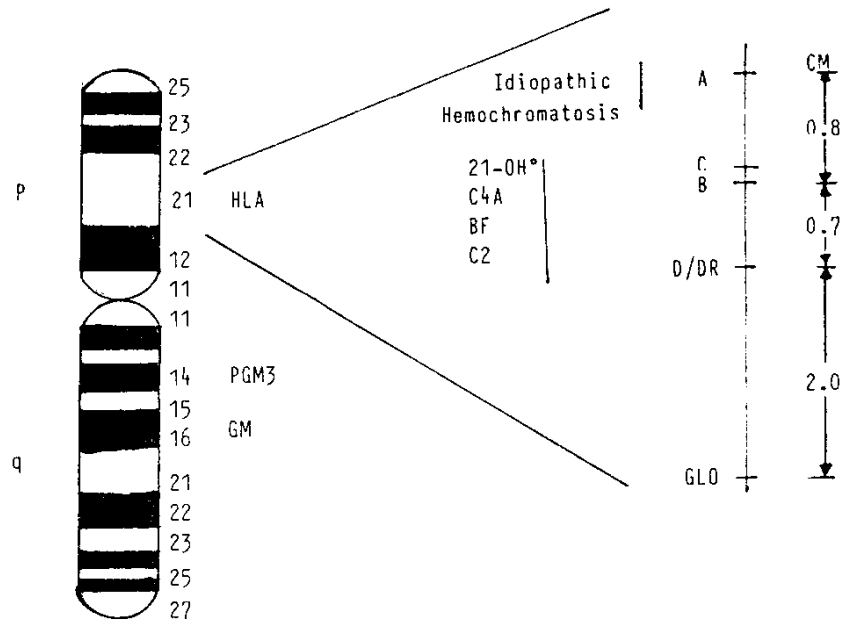

Fig. (1): Showing position of HLA on short arm of chromosome No. 6.

The development of the HLA system has been greatly stimulated by a series of international collaborative workshops started by Amos, 1964. The WHO nomenclature committee meets after each international histocompatibility workshop to review the nomenclature of the antigen in particular with reference to the informations gained

during the workshop. (Mc Devitt and Bodmer, 1974). Originally, the antigens were simply assigned numbers preceeded by HLA, but as the complexity of the system increased it was agreed to use letters for the loci with the prefix HLA reserved to describe the whole system. The letter "w" following a locus symbol indicates that a specificity is still provisionally identified. This designation is removed when there is no further doubt about the clarity and reproducibility of definition of an antigen and when the appropriate antisera are generally available for its definition (Bodmer, 1978).

The Loci of the HLA System:-

Class I antigens:-

They are three clearly defined loci within HLA complex, HLA - A, HLA - B, and HLA - C. They are serologically defined, the A and B loci are recognized as such in 1970, and the C locus was identified shortly after. (Carpenter and Strom, 1980). The class I antigens are present in varying densities in most of body tissues, including B - cells, T - cells and platelets, but not in mature red blood cells. However, it is important to note that there is certain exceptions in the HLA - A, - B and - C distribution in tissues.

Duquesony, et al., (1977), provided that platelets often lack some HLA - B antigens and most HLA - C antigens. Fibroblast and cultured amniotic cells were also reported to be lacking of HLA-B (Pollack,

1979).

Class I antigens have an important role in "self" recognition. They carry foreign determinants important in immune recognition by both alloantibodies and alloreactive cytotoxic T lymphocytes (CTL), and the self-determinants important in immune recognition of virally infected cells by CTL. (Michael et al., 1983). This led to the hypothesis that the class I antigens are physically modified by viral products or that cytotoxic T - lymphocyte must interact with a viral target antigen and a class I molecule in order to be functionally lytic. (Show et al., 1981).

Class II antigens:-

They include HLA - D, - DR, SB, MB and MT antigens. These antigens are expressed only on B - Lymphocytes, macrophages, monocytes and endothelial cells (Chang et al., 1983). Class II HLA molecules on the surface of antigen presenting cells are essential for recognition of antigen by T cells that usually express the T_4 marker and that have been associated with initial recognitive events in a T cell response particularly of cells with helper or inducer activities (Pollck et al., 1985). (Table: 1) showing listing of recognized HLA antigens).

Table.(1): Showing listing of recognized HLA antigens.

HLA-A	HLA - B	HLA-C	HLA - D	HLA - DR
HLA-A1	HLA-Bw4	HLA-Bw42	HLA-Cw1	HLA-Dw1	HLA-DR1
HLA-A2	HLA-B5	HLA-Bw44(12)	HLA-Cw2	HLA-Dw2	HLA-DR2
HLA-A3	HLA-Bw6	HLA-Bw45(12)	HLA-Cw3	HLA-Dw3	HLA-DR3
HLA-A9	HLA-B7	HLA-Bw46	HLA-Cw4	HLA-Dw4	HLA-DR4
HLA-A10	HLA-B8	HLA-Bw47	HLA-Cw5	HLA-Dw5	HLA-DR5
HLA-A11	HLA-B12	HLA-Bw48	HLA-Cw6	HLA-Dw6	HLA-DRw6
HLA-Aw19	HLA-B13	HLA-Bw49(w21)	HLA-Cw7	HLA-Dw7	HLA-DR7
HLA-Aw23(9)	HLA-B14	HLA-Bw50(w21)	HLA-Cw8	HLA-Dw8	HLA-DRw8
HLA-Aw24(9)	HLA-B15	HLA-Bw51(5)		HLA-Dw9	HLA-DRw9
HLA-A25(10)	HLA-Bw16	HLA-Bw52(5)		HLA-Dw10	HLA-DRw10
HLA-A26(10)	HLA-B17	HLA-Bw53		HLA-Dw11	
HLA-A28	HLA-B18	HLA-Bw54(22)		HLA-Dw14	
HLA-A29	HLA-Bw21	HLA-Bw55(w22)			
HLA-Aw30	HLA-Bw22	HLA-Bw56(w22)			
HLA-Aw31	HLA-B27	HLA-Bw57(*7)			
HLA-Aw32	HLA-Bw35	HLA-Bw58(17)			
HLA-Aw33	HLA-B37	HLA-Bw59			
HLA-Aw34	HLA-Bw38(w16)	HLA-Bw60(40)			
HLA-Aw36	HLA-Bw39(w16)	HLA-Bw61(40)			
HLA-Aw43	HLA-B40	HLA-Bw62(15)			
	HLA-Bw41	HLA-Bw63(15)			

Class III (Complement):-

Structural genes for three complement components, C_4, C_2 and Bf (factor), have been mapped to the HLA B-D region. In addition, deficiency states for C_4 and C_2 have been shown to be linked to HLA. There are four alleles of C_2& of Bf, six of C_4 A, and two of C_4 B. (Carpenter and Storm, 1980).

Genetics of HLA System:-

Because of the close linkage of the alleles, their combination at each locus on a single chromosome is usually inhereted as a unit. This unit is reffered to as the "haplotype". Since we inhert one chromosome from each parent, we have two HLA haplotypes. Because all HLA genes are combinant, both alleles at a given HLA locus are expressed, and 2 complete sets of HLA antigens can be detected on cells. (Schwartz et al., 1979).

Following mendelian laws, there is a 25% chance that 2 siblings will share both haplotypes, a 50% chance that they will share one haplotype, and a 25% chance that they will share no haplotype and will be completely HLA incompatible Fig. (2).

Fig. (2):

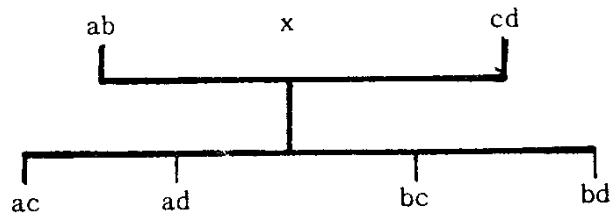

Fig. (2): Inheritance of HLA hapoltypes.

HLA antigens found on the molecule determined by a single allele (and no other) are termed HLA private antigen. In contrast, HLA public antigens are determinents common to several HLA molecules each of which bears a distinct HLA private antigen. HLA-Bw_4 and -Bw_6 are best known examples of HLA public antigens (Shaws et al., 1980).

Linkage disequilibrium:-

Owing to random matings, the frequency of finding a given allele at one HLA locus with a given allele at a second locus should simply be the product of the frequencies of each allele in the population. However, certain combinations of alleles are found with a frequency far exceeding that expected. This phenomenon is termed "linkage disequilibrium". Several hypothesis have been offered in an attempt to explain the phenomenon of linkage disequilibrium including :-

1- a selective advantage of a given haplotype,

2- migration and admixture of 2 populations,

3- Inbreeding, and

4- random drift. (Schwartz et al., 1979).

III. A Typing:-

A. Class I antigen:-

Class I antigens are all defined by serologic reactions, and typing for these antigens is therefore, performed using standard serologic techniques. Typing sera are obtained chiefly from multiparous women. These sera tend to have relatively high titres of antibodies directed against a limited number of HLA determinents. Since in most cases the women has been repeatdely immunized with the HLA antigens of a single individual- the father of her children-which are present on the foetus she carries. Many attempts have been made to produce monoclonal antibodies with high titre and enough specificity for use typing reagents (Ray, 1979).

The most widely used method for HLA typing is Lymphocyte Microcytotoxicity Assay. Fig (3) showing the microcytotoxicity testing for HLA antigens.

- Multiple antisera against HLA-A, -B-and-C antigens are placed in the microwells of a typing tray, and the trays are then frozen untill needed for typing.