MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) AND DISEASE

THESIS

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Master degree in Clinical and Chemical Pathology

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A C K N O W L E D G E M E N T

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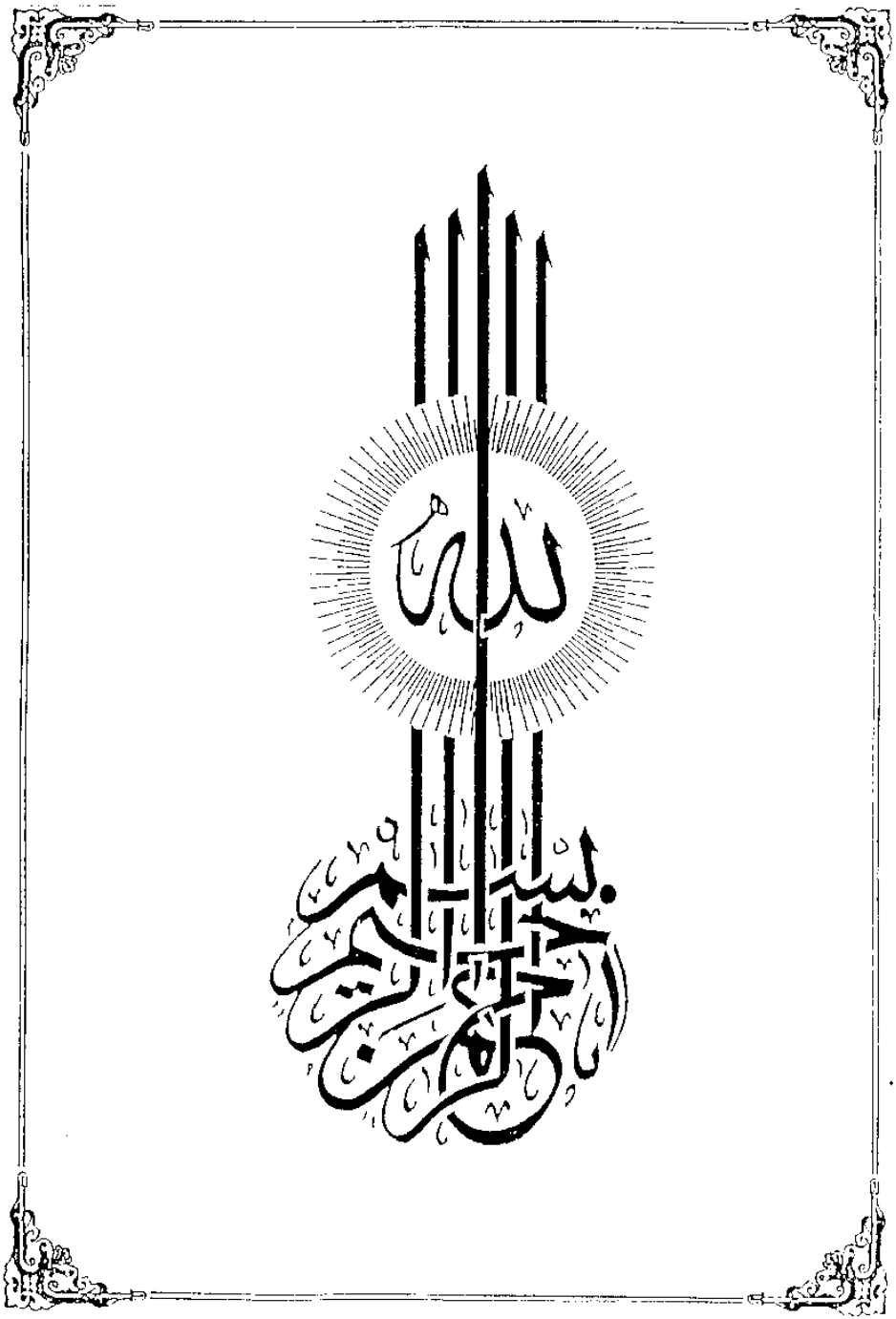

C O N T E N T S

INTRODUCTION AND AIM OF THE WORK

Introduction and aim of the work:

In humans, as in all other mammals there is a chromosomal region containing genes of fundamental importance to immune responses. These genese include, among others, the HLA genes (Herbert, 1980).

A large number of human diseases have been shown to correlate significantly with the presence of certain HLA gene products. These associations are important in understanding the mechanisms of genetic predisposition to disease and the basic role of major histocompatibility complex.

The aim of this work is to make a review concerning HLA antigens, their association with different diseases, and the value of this association as a diagnostic measure.

THE MAJOR HISTOCOMPATIBILITY COMPLEX

The Major Histocompatibility Complex

Histocompatibility Antigens:

Histocompatibility antigens are present on all nucleated cells of the body including leukocytes. They are classified as strong or weak antigens. Those which are more potent are antigens of the major histocompatibility complex, while weak antigens are called the minor histocompatibility antigens (Barrett, 1978).

Minor Histocompatibility Antigens:

They are simply surface structures that can be recognized immunologically. Many, if not most, of these minor antigens have been very difficult to define by in vitro serologic techniques. Much less is known about the genetics, structure and function of minor antigens in comparison to major histocompatibility antigens, it is believed that minor antigens are allotypes of cell surface structures that serve a variety of physiologic functions, and there is little reason to believe at present that they play any special role in immune responsiveness (Klein, 1977; Graff, 1978).

Historical Background:

Early studies, especially by Dausset, revealed white-cell agglutinins in the serum of polytransfused individuals. Such sera were used later on for the definition of the white cell antigens, but these sera turned out to be too complex to be generally useful (Snell et al. 1976).

Further developments based on the discovery by van Rood and Payne in 1958 that leucocyte agglutinins were produced by fetal-maternal stimulation. van Rood in 1962 defined two-allele system which he called "group 4". Payne et al., in 1964 defined an apparently independent allelic system of antigens which they called LA (L for leucocytes and A for the first locus). The LA and group 4 loci, now are known as the HLA-A and HLA-B loci, respectively.

The development of the HLA system has been greatly stimulated by a series of international collaborative workshops started by Amos in 1964. These workshops, which have involved the exchange of reagents amongst a large number of participating laboratories and the combined analysis of the resulting data have each been major turning points in the development of knowledge of all aspects of the HLA system.

The second and third workshops organized by van Rood in 1965 and Ceppellini in 1967 placed the definition of the first described antigen on a firm footing and established that antigens belonged to a single system of closely linked genes (Dausset et al., 1965; Ceppellini et al., 1967).

The fourth and fifth workshops organized by Terasski in 1970 and Dausset in 1972 established the control by two linked loci of the main serological specificities, and through a world wide series of population studies, the universality of this genetic model and the general distribution of the antigens amongst the major human population groups (Sandberg et al., 1970; Dausset & Colombani, 1973).

The sixth workshop was organized by Kismmeyer-Neilsen in 1975 clarified the definition of the third, or, HLA-C serological locus and established the HLA-D locus identified by the mixed lymphocyte culture reaction. (Kissmeyer-Nielsen, 1975).

The seventh of these workshops was organized in 1977 by Bodmer and led to the serological definition of the HLA-DR types, establishing their relationship to the HLA-D type and clarifying their

role in disease association (Bodmer et al. 1978).

International Nomenclature of HLA Antigens:

The main function of the World Health Organization (WHO) nomenclature committee which generally meets after each international Histocompatibility Workshop is to review the nomenclature of the antigen in particular with reference to information gained during the workshop. Each antigen is identified by a letter for the locus which controls it, followed by a number defining the particular specificity of that locus. The letter W indicates that a specificity is still provisionally identified.

Nomenclature for factors of the HLA system after the 8th international workshop in 1980 by the World Health Organization are listed in the table.

HLA Genes & Their Products:

The HLA gene complex is a portion of the short arm of the chromosome 6. Five closely linked genes are present in this chromosomal region: HLA-A, B, C, D and DR. These loci demonstrate an extraordinary degree of polymorphism. It consists of several series of paired alleles which are inherited as a gametic unit on a segment of chromosome called a haplotype (Amos & Yunis, 1979).

An individual who has the same gene or allele at a given locus on both homologous chromosomes is said to be homozygous at that locus, when the two alleles are not the same, the individual is said to be heterozygous. Similarly, an individual can be homozygous or heterozygous for the whole complex, true homozygous being very rare in most populations (Fritz & Marilyn, 1978).

Family Studies:

Each parent contributes to a child one of the 2 chromosomes containing the HLA region. Thus, each child inherits two haplotypes one from each parents. The HLA antigens detected on a cell (phenotype) are

expressed as in the following example: HLA-A1,2; B5, 7; Cw1, w3; Dw2, w3. The genotype consists of 2 haplotypes. The children can inherit only 4 possible combinations. Thus, 2 siblings have a 25 % chance of being HLA-identical, a 50% chance of sharing only one haplotype, and a 25% chance of differing both haplotypes (Herbert, 1980).

Is it invariably the case that each parent transmits one of his or her haplotypes to each offspring? In the HLA system this is true about 99 % of the time. Family studies however, indicate that exceptions, known as recombinants, do occur about 1 % of the time. These exceptions are the consequence of crossing over, which occurs at meiosis (Payne, 1977). An example is shown in Figure (1).

In the central portion, the point of crossover is illustrated.

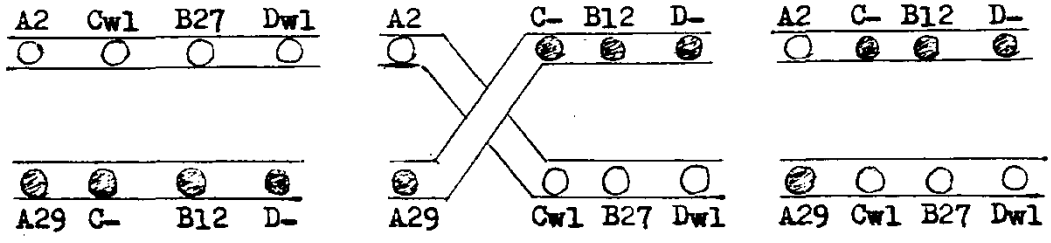

Figure (1) Crossover between A and C loci

Linkage Disequilibrium:

Genes of the HLA region are closely linked, and certain antigen combinations tend to be on the same haplotype of random individuals of a given ethnic group more frequently than would be expected by multiplying the gene frequencies of the individual antigens. For example, the frequency of the gene A1 in one Caucasoid population was 0.19 and the frequency of B8 was 0.16. If they assorted randomly, one would expect that the frequency with which both occurred together on the same cell would be 0.19 x 0.16, or 0.03. However, the calculated frequency of the haplotype A1, B8 in the same population is 0.128. Thus, A1 and B8 appear on the same haplotype significantly more often than would be expected. This is known as linkage disequilibrium. As indicated above, the HLA-DR genes, if different from the HLA-D genes, must have a very high degree of linkage disequilibrium with HLA-D genes. A significant degree of association between a disease and an HLA gene may not necessarily indicate That The HLA gene is responsible for the disease. The disease may be associated with a gene which is in linkage disequilibrium with an HLA gene (Herbert, 1980).

The HLA Antigens

The HLA complex consists of loci with gene products (cell-surface antigens) which can be divided into:

(1) Class I Antigens:

Class I HLA antigens are defined serologically, and each antigen consists of an 11,600 dalton B_2-microglobulin, and a 44,000 dalton heavy chain which carries the antigenic specificity (Springer & Strominger, 1977; Fuks et al., 1977).

HLA antigens are present on the surface of all nucleated cells of the body, spermatozoa, reticulocytes and platelets. HLA antigens are also found in low concentration in plasma and in urine (Fellous & Dausset, 1970; Harris & Zervas, 1969; Dausset et al., 1960).

Three clearly defined loci (HLA-A, B and C) are known within the HLA complex for class I HLA antigens (Klein, 1977). Twenty antigens could be detected at locus A, 42 antigens at locus B and 8 antigens at locus C.

(2) Class II Antigens:

Serologically defined specificities closely related to the D locus, and putative immune responce