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PERSPECTIVES *on* AUTOIMMUNITY

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Perspectives on Autoimmunity

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INTRODUCTION

The objective of this book is to provide the reader with a perspective on salient points in the field of autoimmunity. This book is timely because autoimmunity, like so many other aspects of immunology, is in a process of accelerating evolution in both technology and concepts.

Sir Macfarlane Burnet taught, as a corollary to the Theory of Clonal Selection, that the lack of immune reactivity against the self was founded on the elimination of lymphocytes capable of recognizing self-antigens.[1] Autoimmune disease was believed to develop as a consequence of recognition of self-antigens by immunologically competent lymphocytes that had not been eliminated. According to this view, self-recognition was an aberration punished automatically by autoimmune disease. However, the development of techniques for in vitro culture and activation of antigen-specific lymphocytes led to the finding that healthy animals might indeed be populated with self-recognizing lymphocytes.[2-4] Moreover, the discovery that T lymphocytes recognized antigens in association with self major histocompatibility complex (MHC) molecules[5,6] indicated that at least some sort of self-recognition was physiological.[7] Self-recognition was further legitimized by Jerne who, in his theory of the idiotype-anti-idiotype network, proposed that it played a central role in regulation of the immune system.[8]

Most recently, the field of autoimmunity has benefited from new knowledge obtained through the use of monoclonal antibody technology and the development of functional lines and clones of autoimmune T lymphocytes. These methodologies have made it possible to analyze self-recognition at the level of a single antibody molecule or a single T lymphocyte. In parallel to the advances in immunological technology, autoimmunity research has benefited from progress in microbiology, particularly in an increased appreciation of the persistence of viruses and their effects on the host.

The articles in this book review much of this new information. de Vries and van Rood describe the critical function of MHC genes in regulating the immune response. Naparstek and Schwartz present a theory of autoimmunity that touches upon most of the key problems of the field. Boitard and McDevitt illustrate the immunogenetic and cellular immunology of autoimmune diabetes. Waksman presents a comprehensive view of multiple sclerosis and proposes a new theory to account for the enigma of an organ-specific autoimmune disease for which an organ-specific target antigen may be lacking. Wege and his colleagues recount how virus infection is able to induce autoimmune disease of the nervous system. Schoenfeld's article illustrates the wealth of information that has been obtained applying hybridoma and anti-idiotypic techniques to systemic lupus erythematosis. Stollerman, in telling the story of rheumatic fever, focuses attention on bacteria as inducers of autoimmunity. Holoshitz and his colleagues describe how they have used T lymphocyte lines and clones to elucidate the pathogenesis of adjuvant arthritis, with some reference to rheumatoid arthritis. They also show that it is possible to treat adjuvant arthritis with a suitable T lymphocyte clone. McGuigan and his colleagues analyze contending views of the complicated relationship between bacterial infection, an MHC gene product, and ankylosing spondylitis. Finally, new approaches to therapy are described by Schoenfeld and co-workers; by Steinman and his associates, using antibodies to MHC molecules; and by myself, using T lymphocyte vaccines.[9]

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THE EDITOR

Irun R. Cohen is the incumbent of the Mauerberger Professorial Chair in Immunology, in the Department of Cell Biology of The Weizmann Institute of Science, Rehovot, Israel. Dr. Cohen graduated from Northwestern University, Evanston, Illinois, with a B.A. degree in philosophy (honors) and obtained his M.D. degree (summa cum laude) in 1963 from Northwestern University Medical School, Chicago, Illinois. As a medical student Dr. Cohen had an opportunity to do a research project in the laboratory of Dr. Gene H. Stollerman on virulence factors of Group A Streptococci. The experience of working with Dr. Stollerman awakened Cohen to the excitement of medical research. He interned at Hadassah-University Hospital, Jerusalem, Israel. From 1964 to 1966 Dr. Cohen served as a commissioned officer with the United States Public Health Service at the Communicable Diseases Center, Atlanta, Georgia. He then did a residency in pediatrics on the Harriet Lane Service of the Johns Hopkins Hospital, Baltimore, Maryland, and received board certification in pediatrics. In 1968, Dr. Cohen came to The Weizmann Institute as a post-doctoral fellow with Dr. Michael Feldman, during which time he collaborated with another fellow, Dr. Hartmut Wekerle, to enter the field of autoimmunity. In 1970 to 1973, Dr. Cohen assisted Dr. Moshe Prywes in planning a new Medical School at the Ben-Gurion University of the Negev, Beer-Sheva, Israel, and served as the first Acting Dean of the school. In 1974 Dr. Cohen returned to full-time research at the Weizmann Institute.

Dr. Cohen has published over 170 scientific papers and has been a guest speaker at many universities, institutes, and international research conferences. His major research interests relate to the pathogenesis and control of autoimmune disease.

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Chapter 1

HLA AND AUTOIMMUNITY

René R. P. de Vries and J. J. van Rood

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I. INTRODUCTION AND SUMMARY

It may not be obvious from all the chapters of this book, but the function of the immune system is to confer protective immunity. Protective immunity may be defined as protection against pathogenic microorganisms and other invaders of the organism, i.e., malignant cells, without unnecessary harm to the host. Because the same elements and mechanisms that are used by the immune system to confer protection may also mediate injury of self, the immune system is a dangerous system. It is obvious, therefore, that an extremely well-controlled regulation is essential to confer protective immunity without immunopathology.

One of the main systems regulating the immune response is the major histocompatibility complex (MHC), which is present and similar in all vertebrates studied. The human MHC, or HLA system, is one of the two best studied MHCs. It is the most polymorphic genetic system known, which means that an exceptional interindividual variability is found. HLA class I and II products are essential for T-cell activation and for the regulation of the immune response. Moreover, they are immune response (Ir) gene products because their polymorphism leads to interindividual differences in immune responsiveness. Several factors of the complement system are also coded in the HLA system and are referred to as HLA class III products. They are also quite polymorphic, and also this polymorphism may have functional consequences.

From the foregoing it is obvious that the HLA system may also play a role in the development of autoimmune diseases. This is indeed the case and has important implications for the pathogenesis and management of several autoimmune diseases.

II. HLA AND HEALTH

A. The HLA System[1,2]

The HLA system was originally defined as the human MHC because its products are strong histocompatibility antigens. Especially during the last 10 years it has become clear that this system has considerably more ambitions than frustrating transplantation surgeons. It is now established that its products play a central role in the immune response, and further surprises may be expected in the future. All vertebrates studied appeared to possess an MHC with remarkable interspecies homology of genetic structure, gene products, and function.

The HLA system is situated on the short arm of chromosome 6. As shown in **Figure 1**, it comprises at least three different types of very polymorphic genes: classes I, II, and III. Except for DP,[3] these genes are all situated so close to each other (recombination $< 2\%$) that they are usually inherited together or as a so-called "haplotype". A fourth type of genes (class IV), which is related to class I, is situated 10 to 20 cm to the right of HLA-A.[4,5] The class I, II, and IV genes and their products show striking homologies, while the class III genes and products are totally different.

The degree of polymorphism displayed by the MHC in general and the HLA system in particular is unique in nature. Apart from providing us with a powerful tool for genetic studies, this extreme polymorphism is probably essential for the function of the system, as will be discussed in the next two sections (Sections II.B and II.C). Another genetic characteristic of the HLA system is the phenomenon of linkage disequilibrium: certain combinations of alleles of linked loci occur more (or less) often than predicted from their respective gene frequencies. It is generally assumed that several linkage disequilibria (e.g., as shown by the haplotype DQ2-DR3-C2c-Bfs-C4AQo-C4B1-B8-Cw7-A1) are at least partly the result of selection.[6]

HLA class I molecules are produced by and present on the membrane of basically all nucleated cells. They are glycoproteins consisting of a heavy chain (mol wt 44,000) and a light chain (mol wt 12,000). The heavy chain is encoded by one of three extremely poly-

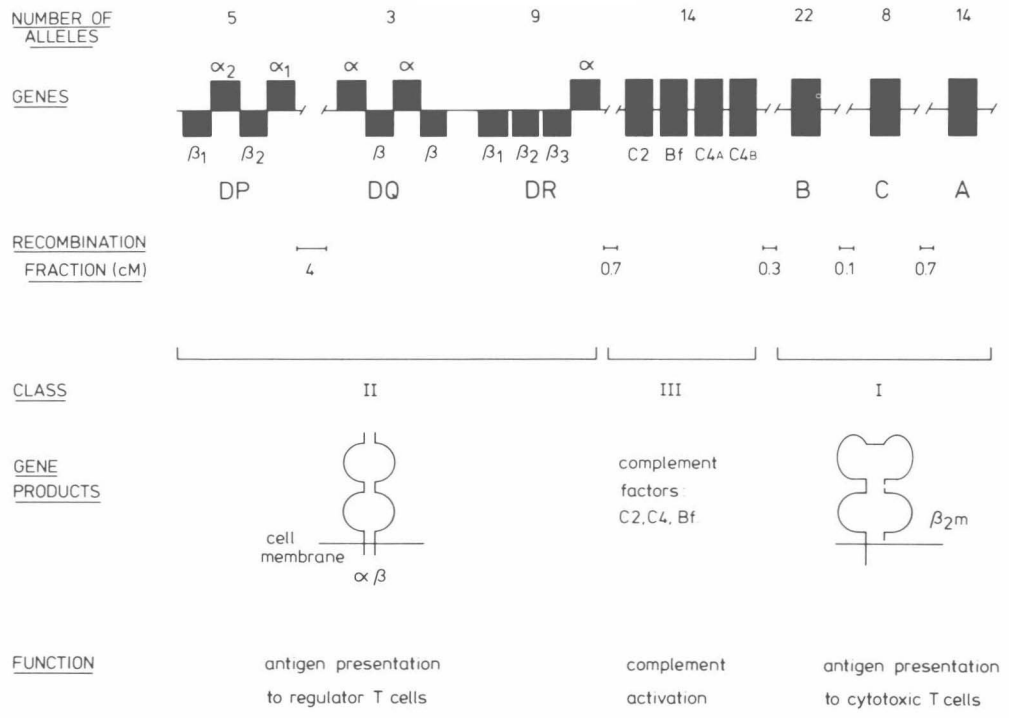

FIGURE 1. The HLA system. Nomenclature is according to the Nomenclature Committee, which met after the 9th International Histocompatibility Workshop in Munich.[3] DP = SB, DQ = MB, DC, or DS.

morphic class I genes (A, B, or C) and the light chain (β_2-microglobulin or β_2m), by a nonpolymorphic gene on chromosome 15. As shown in Figure 1, the heavy chain penetrates the cell membrane, and its extracellular part consists of three immunoglobulin-like domains. β_2m is noncovalently bound to the heavy chain domain which is nearest to the cell membrane. It is interesting that this domain shows marked sequence homology with β_2m, the domains of HLA class II molecules adjacent to the cell membrane (see below), the constant domains of immunoglobulin molecules, and the constant domains of the T-cell receptor for antigen.[7,8] This suggests a common evolutionary origin which may have functional implications.

HLA class II molecules are mainly present on cells of the immune system: macrophages and other antigen-presenting cells, B-cells, and activated T-cells. Other cells may also be induced to express class II molecules by γ-interferon. These molecules consist of two noncovalently associated glycosylated polypeptide chains (α and β). Both chains have two domains, penetrate the cell wall, and are coded by HLA-linked genes. There are five α-genes and seven β-genes known (see Figure 1), and at least three α-genes and five β-genes are expressed as DP, DQ, and DR molecules. We use the nomenclature according to the updating last year of the complicated HLA nomenclature.[3] DP is equivalent to the former SB, and DQ to MB, DC, or DS. Class II β-genes are very polymorphic, whereas the α-genes with the exception of DQ show little or no polymorphism. The DQ α polymorphism may be important because it allows the generation of so-called hybrid class II molecules. Such molecules are composed of an α-chain coded by one and a β-chain coded by the other chromosome (transcomplementation) and increase the DQ polymorphism at the product level in heterozygotes.

Although their relationship to the MHC remains obscure,[9] the HLA-linked genes coding for the complement factors C2, C4, and B(f) are usually referred to as HLA class III genes.

These four genes (C2, Bf, C4A, and C4B) are extremely closely linked to each other and situated between HLA-B and -D. Notably the C4 genes are quite polymorphic, although less than the HLA class I and II genes. The main reason that we mention them here is that it may sometimes be difficult to discriminate between the effect of class I or II and the effect of the closely linked complement genes.

Recently class I related molecules have been detected on human T-cells, which are probably analogous to the murine Qa and TLa molecules.[4,5,10,11] The structure of these molecules seems to be quite similar to that of class I molecules including the molecular association with β_2m. Class IV genes, however, seem to be much less polymorphic than class I genes. They are probably cell differentiation antigens.[10]

There is no doubt that HLA class I and II genes belong to one genetic system, the MHC. As already mentioned, it is unclear whether the closely linked but structurally and functionally different class III genes also belong to this system. Although elegantly speculated upon,[12] no functional relationship with class I and II molecules has thus far been shown for the class III molecules. Until otherwise proven, we favor to consider them as not belonging to the MHC. However, the loosely linked class IV genes almost certainly belong to the system. For instance, there is a coordinated regulation of expression of class I and IV genes.[10,11,13] Finally, we should also mention here that there is at least one gene, i.e., the gene coding for the steroid hormone 21-hydroxylase,[14] which is closely linked to the HLA system, but most probably just got lost there without any functional purposes related to the system. Given these considerations, we will from now on mainly concentrate on the HLA class I and II genes and their products.

B. The Role of HLA Class I and II Molecules in the Immune Response

As mentioned in the introduction, the immune system is a dangerous system, which needs an extremely good regulation. There are basically two regulatory systems: the idiotype network[15] and regulatory T-cells. Both are regulated by antigen. T-cells can only recognize a nominal antigen when it is presented on a cell membrane together with a (self-) HLA class I or II molecule. Therefore, for T-cells "antigen" always means "antigen and HLA class I or II". Apart from being an absolute prerequisite for antigen recognition by T-cells, these HLA products also select the type of T-cells that will respond to a given antigen. Regulator T-cells see (nominal) antigen in combination with HLA class II molecules, whereas cytotoxic T-cells (effector T-cells) see antigen in combination with HLA class I molecules. Different HLA class II products may also determine which regulator T-cells (helper or suppressor) will respond to a given antigen.[16-18] It is thus obvious that both quantitative and qualitative differences in the expression may have a regulatory role in the immune response, and there is increasing evidence that this is the case, indeed.[19,20] There is evidence that the mechanisms regulating this expression are mainly posttranslational.[21] Several molecules mediating the regulation of HLA class I and II expression have been identified: interferons give a positive signal, while E class prostaglandins and -fetoprotein inhibit class II expression.[20]

There is evidence that the T-cell receptor repertoire of an individual is produced in the thymus in the absence of foreign antigens.[22,24] This implies that the T-cell receptor repertoire may be selected by the individual's class I and II products in combination with other autoantigens which happen to be presented by these class I and II products.[15,25,26] It is thus obvious that both multiple class I and II genes and polymorphism of these genes will generate a larger repertoire.

It is clear from the foregoing that HLA (MHC) class I and II genes and their products play an important role in the immune response and its regulation. Of course many questions still remain unanswered. To mention only a few: although there is evidence that (processed) antigen and MHC molecule have to be associated on the membrane of an antigen-presenting cell in order to be recognized by a T-cell,[27,28] it is still far from clear how this association

occurs. This relates to another crucial question: does the T-cell receptor see the combination of nominal antigen and self-MHC, and if so, how? Why do (activated) B-cells and activated T-cells carry class II molecules: to present antigen and perhaps even T- and B-cell idiotypes to (other) T-cells?

Apart from this established function of class I and II molecules in the presentation and elimination of cell-bound antigens, there is evidence that they might affect the immune response in at least one other way. Before an antigen can be presented it has to be bound to and processed by an antigen-presenting cell.[20,27,29] There is increasing evidence that MHC molecules may also play a role in the binding of antigen to a cell. This has been documented for several viruses and both class I and II molecules.[30-32] Bacteria,[33-35] drugs,[36,37] and endogenous substances, i.e., γ-type endorphins,[37] may bind to class I molecules with a preference for certain alleles. As will be discussed later (Sections III.C and III.E), this differential binding correlates with in vivo phenomena.[33,36,37] Moreover, class I molecules have been found to be associated on the cell membrane with receptors for insulin and epidermal growth factor.[38] Such a substance bound to an HLA molecule may then either be internalized[30] or induce an (associated) receptor to trigger an intracellular response. It is clear that such a receptor-like function does not need to be confined to immunological processes, and it is conceivable that the specialized antigen presentation function of class I and II molecules has evolved from a primitive receptor-like function of MHC (class IV?) molecules.[39]

C. HLA Class I and II Ir Genes

Ir genes contain the information for differences in immune reactivity among apparently healthy individuals.[40] This concept boosted by the following two observations made immunogenetics to a new discipline: (1) the demonstration by McDevitt and Benecerraf[41,42] that the MHC contains Ir genes and (2) the observation by Lilly et al.[43] that the same MHC controls resistance to virus-induced leukemogenesis. This led to the idea that these MHC-linked Ir genes might be relevant in real life. At first, the known histocompatibility antigens were only thought to be markers for Ir or disease susceptibility genes. The next important discovery was the demonstration that the class I and II molecules were themselves the products of the coveted Ir genes[44-48] and that their polymorphism was of biological significance.

HLA class I and II Ir genes may work through at least two mechanisms, which are certainly not mutually exclusive. The first mechanism works at the level of the antigen-presenting cell: class I and II alleles differ in their ability to present certain antigens to T-cells, which are equipped with the appropriate receptor for that antigen and the presenting class I or II allele. As discussed in the previous section this difference may be either due to quantitative differences in expression of the different alleles or qualitative differences leading to more or less effective association of the (processed) antigen and class I or II alleles.[19,20,44-48] The second mechanism is that class (I? and) II Ir genes generate the T-cell repertoire of an individual in the thymus, and their polymorphism will generate repertoires that differ among individuals. Evidence for this mechanism is more difficult to obtain, but has been provided.[22,23] At least for the class II restricted repertoire this second mechanism may work basically the same as the first, the (auto-) antigen-presenting cells being in this case the accessory cells in the thymus.[24-26,49,50]

The extreme polymorphism and maybe some of the striking linkage disequilibria shown by the HLA system are at least partly due to selection.[6] Infectious diseases are the most obvious candidates as the responsible selective force. Whatever the mechanism of class I and II Ir genes, it is easy to envisage that a high degree of polymorphism is advantageous not only for the individual, but may be even more for the species surrounded by many different and always changing pathogens.

Linkage disequilibria may thus be due to the fact that certain combinations of alleles work more efficiently and provide a better chance to survive. There is evidence in support of this

hypothesis,[51,52] and the following example may serve to illustrate this. In the middle of the last century a group of Dutch farmers and their families sailed to Surinam (Dutch Guyana) in order to start a new life. However, an epidemic of typhoid fever struck them upon arrival, and within 3 months one half of them had died. A few years later a yellow fever epidemic took the lives of 20% of the survivors of the first epidemic. The remaining settlers mainly intermarried, which gave us the opportunity to compare the frequencies of a large number of polymorphic genes with those of the Dutch people who had stayed in Holland.[52] The results showed that out of 26 polymorphisms studied, only three were significantly different: HLA, Gm (immunoglobulin allotypes), and C3 (third factor of complement).

Such studies are not easy to perform. Moreover, we can only look at known infectious diseases, which only became important some 5 millenia ago.[53] The evolution of the HLA system and the MHC certainly took much longer. Extremely polymorphic MHC-like structures have been found in unicellular organisms, e.g., botryllus Schlosseri,[54] where they act as cell adhesion molecules. Therefore, it might well be possible that both the specialized function in the immune response and the subsequent selection by infectious diseases have been superimposed upon an already existing polymorphic cell communication system.

III. HLA AND AUTOIMMUNE DISEASES

A. The Immunogenetic Approach to Autoimmune Disease

We will start the second part of this chapter with a question: What has immunogenetics to offer for the prevention or treatment of autoimmune diseases? This question may be answered by using the HLA class I and II Ir genes just described as an example. The aim of the immunogenetic approach to an autoimmune disease is to unravel the following chain of events: polymorphic Ir-genes (1) contain the information for Ir gene products (2) which regulate the immune response and differ among individuals. These differences lead to differences in immune reactivity among individuals (3), which in their turn cause differential susceptibility to or expression of autoimmune diseases (4). Possibilities for intervention at each level (1 through 4) are feasible and may lead to preventive or therapeutic applications. The power of this approach lies particularly in the use of Ir gene differences among *healthy* individuals as a probe for a mechanism leading to autoimmune disease, in a similar way as the study of immune-deficient individuals led to a better insight into how the immune system prevents disease. The potential usefulness of this approach is illustrated in several animal models discussed in other chapters of this book (Chapters 11 and 12). Here we will discuss the state of the art in humans.

B. Association between HLA and Autoimmune Diseases

In Table 1 are listed most established associations between immunopathological diseases and HLA. As may be seen most of them have an established or strongly suspected autoimmune pathogenesis, but to complete the picture we have also included diseases such as coeliac disease and dermatitis herpetiformis which are probably due to an aberrant response to a known foreign antigen (gluten). In fact, this table contains most of the established associations between HLA and disease.[55] The antigen frequencies of the associated HLA antigens are given together with two measures for the strength of the association: the relative risk is a measure for the individual risk to get the disease and denotes how much more frequently the disease is seen in individuals carrying the associated antigen as compared to individuals lacking it. The etiological fraction indicates how much this HLA-associated factor contributes to susceptibility for a given disease at the population level.[55]

It is striking that most of the associations are with HLA-DR or class II antigens, and notably all established autoimmune diseases are in this category. This may be explained by the fact that class II antigens are recognized by regulator T-cells as discussed previously.

Table 1
ASSOCIATIONS BETWEEN HLA AND IMMUNOPATHOLOGICAL DISEASES

Disease	HLA	Frequency (%)		Relative risk	Etiological fraction
		Patients	Controls		
Behcet's disease	B5	41	10.1	6.3	0.34
Ankylosing spondylitis	B27	90	9.4	87.4	0.89
Reiter's disease	B27	79	9.4	37.0	0.77
Acute anterior uveitis	B27	52	9.4	10.4	0.47
Subacute thyroiditis	B35	70	14.6	13.7	0.65
Dermatitis herpetiformis	DR3	85	26.3	15.4	0.80
Coeliac disease	DR3	79	26.3	10.8	0.72
	DR7	Also increased			
Sicca syndrome	DR3	78	26.3	9.7	0.70
Idiopathic Addison's disease	DR3	69	26.3	6.3	0.58
Grave's disease	DR3	56	26.3	3.7	0.42
Insulin-dependent diabetes	DR3 and/or 4	91	57.3	7.9	0.80
	DR2	10	30.5	0.2	—
Myasthenia gravis	DR3	50	28.2	2.5	0.30
SLE	DR3	70	28.2	5.8	0.58
Idiopathic membranous nephropathy	DR3	75	20.0	12.0	0.69
Multiple sclerosis	DR2	59	25.8	4.1	0.45
Goodpasture's syndrome	DR2	88	32.0	15.9	0.82
RA	DR4	50	19.4	4.2	0.38
Pemphigus (Jews)	DR4	87	32.1	14.4	0.81
Hydralazine-induced SLE	DR4	73	32.7	5.6	0.60
Postpartum thyroiditis	DR4	72	32.2	5.3	0.58
Hashimoto's thyroiditis	DR5	19	6.9	3.2	0.13
Pernicious anemia	DR5	25	5.8	5.4	0.20
Juvenile RA	DRw8	23	7.5	3.6	0.17
Primary glomerulonephritis	C4B*2.9	25	1.5	22.0	0.24

Adapted from Svejgaard, A., Platz, P., and Ryder, L. P., *Clin. Immunol. Allerg.*, 4, 567, 1984.

Looking at the associated HLA-DR antigens, it is further striking that HLA-DR3 appears so often.

Why all these associations? As elegantly worded by the editor of this book: it may be advantageous to be a low responder.[56] Therefore, these diseases might be the exceptions that prove this rule. However, the ''autoimmune'' DR3 haplotype is one of the HLA haplotypes showing the strongest linkage disequilibrium, which is almost certainly due to natural selection. So, the DR3-containing haplotype in all probability has had selective advantages. We have discussed that virulent pathogenes may have been important selective forces for the evolution of the HLA system. Although there is no actual proof for the DR3 haplotype, we believe that these virulent pathogens may have selected haplotypes conferring a relatively aggressive immune response.[52] These might then become harmful in the presence of less virulent pathogenes or other subtle antigenic changes and thus confer susceptibility to autoimmune diseases. Another possibility is that a low response is also advantageous for some or maybe even many infectious diseases. The DR3 haplotype might then be a low-responder haplotype and the association with autoimmune diseases due to, for example, persistent infection with certain viruses. In both cases such haplotypes might not disappear soon if the disadvantage is expressed as morbidity later in life rather than decreased Darwinian fitness, as is the case for nearly all HLA-associated immunopathological or autoimmune diseases. In other words: we think that the association between HLA and these immunopathological diseases is to be considered as the other side of a coin made to confer immunity.