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Lymphocytes. 1 Function

Genetic restrictions in the immune response

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The aim of this short review is to describe the role of the major histocompatibility complex (MHC) in the regulation of T lymphocyte function.This genetic complex, which includes the immune response (Ir) genes, imposes certain restrictions on the immune system. The clinical relevance of these findings is indicated by the well-known associations between particular HLA antigens and disease susceptibility. An abnormal immune response appears to play a major role in the pathogenesis of many of these diseases.

It should be emphasised that several other aspects of the immune response show inherited variability. Macrophages are probably the first cells to react with a foreign antigen. After some form of processing, possibly partial digestion, antigen is presented on the cell surface to T lymphocytes. B lymphocytes bind antigen to their surface (receptor) antibody and interacting with helper T cells divide and differentiate into antibody-producing cells. T helper cells also stimulate precursors of effector T lymphocytes to differentiate and are themselves modulated by a third type of T lymphocyte, the suppressor cell.

The function of each of these cell types is subject to genetic variability. Macrophages in mice bred selectively for vigorous humoral immune responses bind antigen more efficiently than those from mice bred for low antibody responsiveness (Wiener and Bandieri, 1974). Inherited defects in T lymphocyte functions are known to vary from failure of thymus development in nude mice to single enzyme deficiencies (Giblett *et al.*, 1975). A selective deficiency in suppressor T lymphocyte function has been demonstrated in mice of the New Zealand Black strain, which are subject to multiple autoimmunity (Allison *et al.*, 1971). Inherited abnormalities of B cell function may be generalised, as in the Bruton type of agammaglobulinaemia, or confined to a single immunoglobulin class. A high level of serum IgE, which may result in multiple allergies, is also under simple genetic control (Marsh *et al.*, 1974). In all of these examples the variability in the immune response is not specific for individual antigens.

Antigen specificity in immune responses is determined primarily by antibody. The antigen receptor of B lymphocytes is antibody, and there is increasing evidence that the T lymphocyte receptor includes the variable regions of immunoglobulin heavy chains (reviewed by Eichmann, 1976; Krawinkel *et al.*, 1977). The nature of the remainder of the T cell receptor is unknown.

Genetic defects in B and T cell function that are antigen specific could therefore be due to lack of appropriate antibody molecules. An immunoglobulin molecule is composed of heavy (H) and light (L) chains, each of which has a constant (C) and variable (V) part under separate genetic control. The variable regions (V_H and V_L) include the antigen binding site. Each individual can make at least 10^6 different antibody molecules, each with unique specificity for antigen—that is, $V_H : V_L$ pairs (reviewed by Williamson, 1976). Each molecule can bind a range of antigenic determinants with varying affinity. The number of antigens recognisable by one individual therefore is vast, and nearly all biological macromolecules elicit an antibody response composed of several different antibody species (a polyclonal response). Provided certain requirements for size are met and an appropriate carrier protein (recognised by helper T cells) is used, almost any organic molecule can stimulate an antibody response. Those that do not do so tend to fail in all members of the species. The repertoire of antigen-binding sites available therefore seems to be very similar between all individuals. Differences in antibody quality may be detected, however. Mice of the C57 strain make antibody to the hapten NP (4-hydroxy 3-nitrophenyl acetyl) that has higher affinity for the related hapten NIP (4-hydroxy-5-iodo-3 nitrophenyl acetyl) (Imanishi and Mäkelä, 1975).This unusual characteristic, which reflects a particular conformation of amino-acids at the binding site, is inherited as a trait linked to an immunoglobulin constant region genetic marker, or allotype. As V and C genes are genetically linked, this means that the fine specificity of this antibody is determined by an inherited germ

line V gene. The antibody response to this hapten in C57 mice is dominated by one antibody species with this unique variable region (McMichael *et al.*, 1975). Similar results have been found with some other antigens (Blomberg *et al.*, 1972; Hansburg *et al.*, 1977; Mäkelä *et al.*, 1978). Small, genetically determined, differences in antibody affinity for particular antigens between individuals may be clinically important in determining whether immune complexes are formed (Passwell *et al.*, 1974).

If the T cell receptor is also antibody one might expect the range of antigens recognised by T cells to be as great as that 'seen' by B cells. Paradoxically this is not the case (reviewed by Paul and Benacerraf, 1976). This may, in part, be because the T cell receptor has been shown only to include V_H products so that there may be no associated V_L. If so, examples of T lymphocyte responsiveness linked to immunoglobulin heavy chain polymorphisms (allotypes) would be expected. In fact, variability of T cell function is genetically linked, not to immunoglobulin allotypes but to the major histocompatibility complex. This does not control immunoglobulin structure and has been mapped to a different chromosome.

The critical role of histocompatibility products in immune responses was first demonstrated in mice (Benacerraf and McDevitt, 1972). The amount of antibody produced on challenge with synthetic peptide antigens was shown to be controlled by immune response (Ir) genes that mapped in the major histocompatibility complex (MHC). High responsiveness was dominant. Ir genes have since been shown to control humoral immune responses to many, if not all, protein antigens and also certain cellular immune responses (Gordon and Simpson, 1977; Schmidt-Verhulst and Shearer, 1975). Thus each individual (mouse) has its immune response to a large series of antigens controlled by MHC products. The level at which Ir genes operate appeared to be on the T helper cell recognition of macrophage associated antigen (Benacerraf and McDevitt, 1972). It is now apparent that the recognition of cells and foreign antigens by the other T lymphocyte subpopulations (suppressor and cytotoxic T cells) is also controlled by the MHC.

Although these results were obtained in experimental animals, the same phenomena are now being described in humans (Greenberg *et al.*, 1975; Bergholtz and Thorsby, 1977; Goulmy *et al.*, 1977; Dickmeiss *et al.*, 1977). In this review I shall base the discussion on the results of our experiments on the role of HLA antigens in cytotoxic T cell function (McMichael *et al.*, 1977; McMichael, 1978). These results, which illustrate the restrictions placed on immune responses by the MHC, support a hypothesis that explains the mechanisms involved and how Ir genes work.

Cytotoxic T lymphocytes

The natural function of cytotoxic T lymphocytes (CTL) is probably to eliminate virus infected cells. Virus is thus destroyed before it has been assembled in the cell or on its surface. Their importance in control of human virus infection is indicated by the normal recovery from and immunity to viral infections such as influenza in patients with agammaglobulinaemia.

Human CTL specific for influenza virus have been studied *in vitro* (McMichael and Askonas, 1978). Lymphocytes from volunteer donors were sensitised *in vitro* with autologous lymphocytes that had been infected with the virus. The surface of the latter cells differed from normal in the presence of influenza virus proteins in the membrane. No CTL were present before sensitisation and a period of culture for at least four days was essential for their generation. Virus-infected cells or inactivated virus were essential to stimulate the generation of CTL. As all donors had at some time suffered from influenza virus infection this sensitisation *in vitro* may be regarded as a secondary immune response. The cells with cytotoxic activity were shown to be T lymphocytes and lysed target cells directly without the intervention of antibody.

CTL activity was measured by testing the cultured lymphocytes on freshly prepared peripheral blood lymphocytes that had been infected with influenza virus and radiolabelled with sodium chromate-51. Lysed cells released ^{51}Cr into the medium, which was measured in a gamma counter.

The CTL showed specificity for virus. This was shown by sensitising two samples of blood lymphocytes, from one donor, to influenza A and B in parallel. The CTL generated showed specificity for the sensitising virus type A or B (Fig. 1).

The CTL also showed specificity for the HLA type of the target cell. This is illustrated by the experiments shown in Fig. 2. CTL prepared from C.W.'s lymphoctyes lysed only target cells from donors that shared his HLA A or B antigens. Target cells that shared his HLA D antigens or no HLA antigens were not lysed. Similar results to these have been found for CTL specific for many viruses in the mouse (Doherty *et al.*, 1976). As with the human, many of the viruses studied have been pathogenic to mice—for example, LCMV and ectromelia (Zinkernagel and Doherty, 1974; Gardner *et al.*, 1975). The regions of the mouse histocompatibility complex (H-2) involved are the K and D products which are chemically homologous with the human HLA A and B antigens.

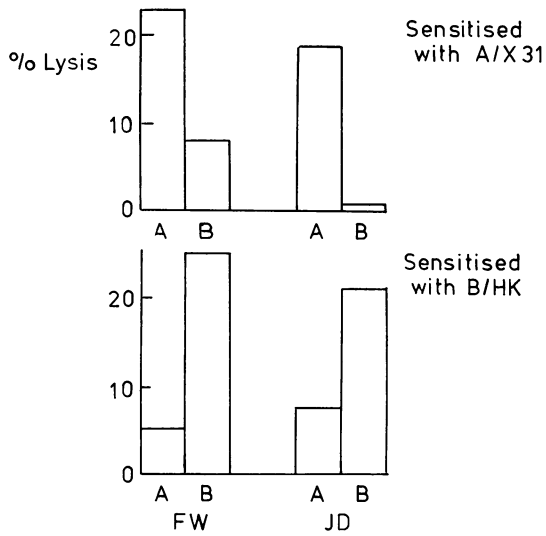

Fig. 1 *Human CTL show specificity for virus. Two experiments are shown for CTL generated from lymphocytes from F.W. and J.D. In each case lymphocytes were sensitised to autologous cells infected with influenza A/X31 (upper panel) or influenza B/HK (lower panel) and then tested for cytotoxicity on autologous cells infected with either influenza virus A/X31 (A) or B/HK (B).*

These results mean that for CTL to lyse target cells they must recognise both their surface viral antigens and HLA A or B antigens.

Two interpretations of these results have been proposed (Zinkernagel and Doherty, 1974). In the first model the T cell may interact only with cells that share its own HLA antigens through a special self receptor. Alternatively, the CTL precursor at the start of the culture period recognises a combination of HLA antigens and cell surface viral antigen on the (autologous) sensitising cell and the mature CTL must see the same combination to lyse the target cell. In the first of these hypotheses there would be two receptors (which could be different regions of a single molecule), one for foreign antigen and one for self HLA. In the second model a single receptor would see the result of an interaction between HLA antigen and virus antigen. This could be either a complex, an alteration of HLA by the virus (altered self), or a specific orientation of virus antigen by the HLA antigen.

Although it is not possible to distinguish unequivocally between these two models and their variants the single receptor hypothesis is simpler and appears to fit the available data more easily, particularly the following results.

Certain histocompatibility antigens fail to interact with particular virus products to generate CTL. This

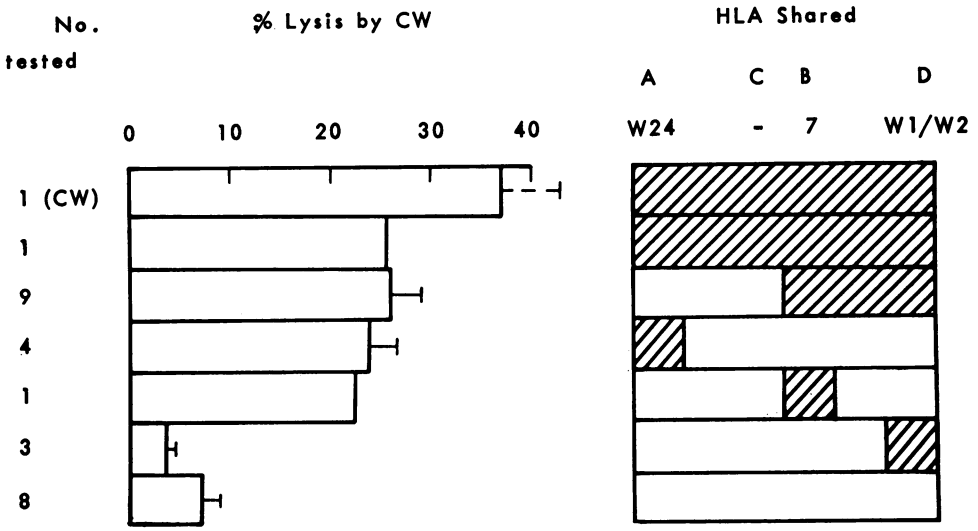

Fig. 2 *Restriction of human cytotoxic T lymphocyte (CTL) activity by the HLA system. C.W.'s lymphocytes were sensitised* in vitro *with influenza virus-infected autologous lymphocytes to generate CTL. These were tested on influenza virus-infected target cells prepared from C.W. and 26 unrelated individuals. Although tested separately the results are grouped according to the degree of HLA antigen-sharing with C.W. The HLA type of C.W. was AW24, W24, B7, 7, C−, −, DW1, W2 and the degree of sharing by the target cells is shown as cross hatching. Results are shown as mean per cent lysis of target cells for each group. (Figure reproduced by permission of the editors of the* Journal of Experimental Medicine.)

has been found for influenza virus antigens on infected human cells that carry HLA A2 (McMichael, 1978). When influenza-specific CTL were prepared from donors that possessed HLA A2 they lysed targets that were infected and which shared other HLA antigens but not those that shared only HLA A2. (Fig. 3). Although it has not yet been possible to develop human CTL specific for other viruses, and so determine whether this 'deficiency' associated with HLA A2 is virus specific, HLA A2 has been shown to be an HLA antigen that permitted lysis of chemically altered cells by appropriately sensitised CTL (Dickmeiss *et al.*, 1977). The effect with HLA A2 thus seems to be antigen specific and can be most easily explained as a failure of interaction between HLA A2 and influenza virus antigen. Most of the other HLA antigens tested (for example, HLA B7) are effective in allowing (or aiding) lysis of target cells infected with this virus.

Similar results have also been described in the mouse by Zinkernagel *et al.* (1978) for vaccinia and LCMV, and by Doherty *et al.* (1978) for influenza and vaccinia. Thus the murine histocompatibility antigen H-2K^b fails to associate with influenza viral

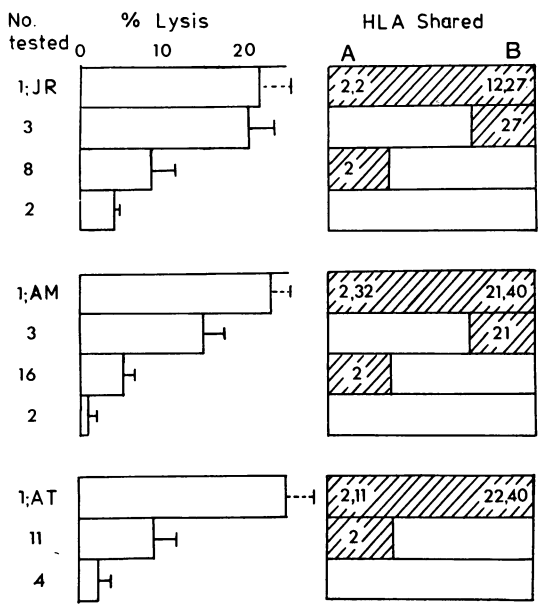

Fig. 3 *Poor lysis of influenza virus-infected target cells that share only HLA A2 with CTL. CTL were prepared from lymphocytes of J.R., A.M., and A.T. and tested on several unrelated influenza virus-infected target cells. The latter are grouped according to the degree of HLA antigen-sharing with the CTL, indicated by cross hatching. Results are shown as mean ± SE lysis for each group. (Figure reproduced by permission of the editors of the* Journal of Experimental Medicine.)

antigens in the development of CTL but does associate with vaccinia (Doherty *et al.*, 1978).

The most extreme examples of histocompatibility antigen specificity for a virus are H-2D^b and H-2K^k, which are the only murine H-2 antigens that associate with Friend leukaemia virus (FLV) to induce CTL (Blank and Lilly, 1977). Furthermore, Bubbers *et al.* (1978) have shown that FLV, isolated from H-2b mice, had incorporated H-2D^b into its coat but not the closely related antigen H-2K^b. In a survey of FLV particles grown in several mouse strains H-2K^k was the only other H-2 antigen detected.

Helenius *et al.* (1978) have shown that Semliki Forest virus coat protein binds specifically to HLA and murine H-2 antigens, but this complex has not yet been shown to generate CTL.

These results indicate that there can be complex formation between histocompatibility antigens and virus products and that one can show specificity for the other. The main difficulty with proposing this as a general phenomenon is to explain how one HLA antigen could interact with many different viruses. One possibility is that the molecule might be somewhat prone to conformational changes which can be induced by new cell surface proteins. The altered HLA antigen would then be recognised as foreign. It is not surprising therefore that some cross-reactivity between histocompatibility antigens altered in this way and those altered by mutation (that is, other 'types') has been observed (Burakoff *et al.*, 1976).

If the hypothesis that there is a single T cell receptor for a virus-HLA complex is correct it is possible that one HLA antigen might interact in an immunogenic way with a group of viruses but not all viruses. Thus HLA A2 though 'poor' for influenza may be 'good' for other pathogenic viruses. It is therefore advantageous for an individual to have as many HLA types as possible—that is, to be heterozygous and to have duplicated HLA loci in the genome. The extreme polymorphism of the HLA A and B antigens could have been generated and maintained in this way.

Helper T cells

The role of MHC products in the function of T helper (TH) cells can be explained in a similar way. Katz *et al.* (1973) showed that T_H cells will co-operate in a secondary immune response only with B lymphocytes derived from mice that shared H2-I region (Ia) antigens with the T cell donor (Ia ≡ HLA DR). Macrophages are also involved in T_H – B cell interactions, and it has been found that the macrophage must also share their Ia antigens.

This particular cell interaction has been extensively investigated in guinea-pigs and mice (Paul *et al.*, 1977). T lymphocytes (almost certainly T_H cells) from immune mice or guinea-pigs proliferated *in vitro* when incubated with macrophages that had been briefly exposed to antigen. The proliferation was abolished by treatment of the macrophages with anti-Ia antibody (Shevach *et al.*, 1972). As T_H cells do not express detectable amounts of Ia antigen on their surface it seemed possible that T_H cells might recognise antigen plus Ia together on the macrophage. Thus the requirement for Ia identity between T_H cells and macrophages would reflect the memory of T_H cells for their priming antigen contact, which was *in vivo* and therefore with 'self' Ia antigens. This was tested by priming T_H cells *in vitro* with allogeneic macrophages plus antigen. On secondary challenge these T_H cells responded to antigen presented on the allogeneic macrophages but not to antigen on autologous macrophages (Thomas and Shevach, 1977). This result indicated that the T_H cells recognised antigen plus Ia on the macrophage cell surface. B cells would present the same combination of antigen and Ia on their surface, and would be recognised and triggered by the activated T_H cells. Thus T_H cells primed with macrophages of one histocompatibility type, plus antigen, stimulated only B cells of the same type to make antibody (Swierkosz *et al.*, 1978).

The way in which T_H cells recognise antigen is therefore reminiscent of the way that CTL recognise antigen, the main difference being the region of the histocompatibility complex involved. These genetic restrictions on T_H activity were originally described in experimental animals but there is increasing evidence that human T_H cells react in the same way (Bergholtz and Thorsby, 1977).

If this concept of T_H recognition of macrophage-bound antigen is correct then an Ir+ gene (that is, in a responder) would be associated with an Ia antigen that interacts with the antigen in question, X, and an Ir− gene (that is, in a non-responder) would be associated with an Ia antigen that fails to form an immunogenic complex (cf. the CTL results). Strong support for this hypothesis comes from Rosenthal *et al.* (1977), who have studied the immune response to different species of insulin in guinea-pigs, in which these responses are under simple Ir gene control. T_H cells from animals that were F_1 hybrids between high and low responders (and therefore phenotypically were high responders, since responsiveness is dominant) responded only to insulin presented on the macrophages derived from the high responder (or F_1) strain. As low-responder macrophages plus insulin did not trigger an immune response in F_1 T_H cells, this result shows that the Ir gene specificity depends on the way in which macrophage presents antigen. The simplest explanation, therefore, is that the Ia antigens are the Ir gene products. One type of Ia antigen on macrophages would form immunogenic complexes with a group of antigens but not all antigens. This Ia type therefore would be associated with positive responses to a series of antigens. This obviates the requirement for a series of Ir genes, each specific for an antigen, in linear array in the histocompatibility gene complex.

Ir genes defined in animals have been specific for antigens of relatively simple structure or for genetic variants of serum proteins (for example, insulin). More complex antigens have multiple antigenic sites, each of which may be under Ir gene control and any one of which may trigger T_H cells. At limiting antigen doses, however, the Ir genes probably determine at what threshold level the immune response is turned on, and this could be clinically important.

Suppressor T cells

The genetic restrictions on suppressor T (Ts) lymphocytes are not so clearly defined. T_S cells that are antigen specific appear to act on cells of the T_H type. In some instances they show specificity for the Ia type of the T_H cells. This has been found in mice (Tada *et al.*, 1975; Rich and Rich, 1975) and in man (Engleman *et al.*, 1977). The picture is complicated by suppressor factors secreted by suppressor cells that carry I region (of the I-J or I-C subregion) determinants and transfer the antigen specificity between cells *in vitro* (Theze *et al.*, 1977). In some instances the suppressor factors show a restriction for the antigen type of the T cell on which it acts (Tada *et al.*, 1975). Immune suppression genes which map in the I region have also been described. It is difficult at present to fit the T_S cell into the generalised scheme proposed for T_H and CTL. It may recognise antigen in a different way, but it clearly involves Ia antigens and is under MHC control.

Role of the thymus in genetic restriction

Recent experiments by Zinkernagel have shown that the restrictions imposed on T cell function by the MHC are controlled by the thymus. Investigating the development of CTL specific for vaccinia virus in mice, Zinkernagel *et al.* (1978) showed that the T cells were 'taught' which histocompatibility antigens to recognise as self in the thymus. In these experiments, described in Fig. 4, bone marrow cells from a mouse that was an F_1 between strain A and B (of different H-2 types) were injected into an irradiated thymectomised F_1 (A × B) recipient. When these

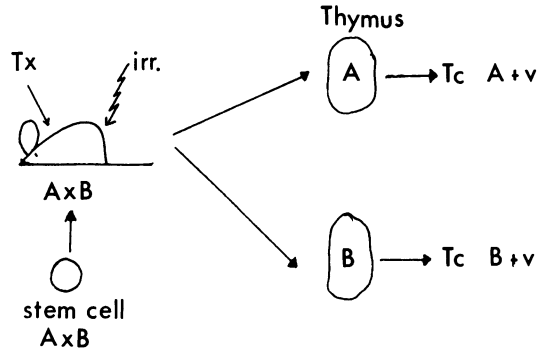

Fig. 4 *The thymus determines the histocompatibility antigens recognised by T lymphocytes. Stem cells from bone marrow of mice that were F1 hybrids between mouse strains A and B, with different histocompatibility types, were injected into irradiated thymectomised (A × B) F1 mice. The mice were also reconstituted with thymus epithelium derived from either strain A or B. They were later infected with vaccinia, and their lymphocytes were then tested for lysis of A or B target cells infected with vaccinia (v). The cytotoxic T lymphocytes (Tc) lysed only the infected target cells that were histocompatible with the thymus graft. Normal (A × B) F1 cytotoxic T lymphocytes can lyse either A or B infected target cells. (Diagram based on experiments by Zinkernagel* et al. *(1978).)*

recipients were reconstituted with parental A thymus the developing CTL, after stimulation with virus, recognised only vaccinia-infected A target cells; when given B thymus they lysed only infected B strain target cells. Normal F_1 CTL would lyse both A and B target cells.

These results, confirmed by Fink and Bevan (1978), and von Boehmer *et al.* (1978) are reminiscent of a proposal by Jerne (1971) that developing lymphocytes acquire their ability to recognise foreign antigen in the thymus. Adapting this hypothesis slightly, it is possible that the immature thymic T cell, which may itself express no HLA antigens (McMichael *et al.*, 1979) is exposed to thymic epithelium which carries HLA ABC and D antigens. According to Jerne, T cells carry receptors for histocompatibility antigens of the species only. T cells responding to self start to proliferate and are destroyed unless they mutate to recognise variants of self histocompatibility antigens (altered self). T cells specific for non-self histocompatibility antigens pass through the thymus but may also be generated by mutation.

Herein lies one problem with the altered self hypothesis of antigen recognition by T cells. It appeared that altered A histocompatibility antigens did not cross react with altered B histocompatibility antigens. This seems to be true to the H-2 antigens chosen by Zinkernagel in his experiments but recent data from Doherty and Bennink (1979) indicate that cross-reactivity can occur. In complicated experiments in which alloreactive T cells had to be removed mature $H\text{-}2^d$ T cells recognised $H\text{-}^k$ virus-infected cells in a restricted manner when they had been primed with virus in an $H\text{-}2^{d/k}$ mouse. These T cells came originally from an $H\text{-}2^d$ mouse. and were therefore educated in an $H\text{-}2^d$ thymus.

The simplest explanation for all the data relating to CTL and T_H cells therefore is that they react to self histocompatibility antigens altered by foreign antigen. This view, however, is not universally accepted and alternative models have been cogently argued (Blanden and Ada, 1978). It is difficult to explain antigen specificity associated with particular H antigens, or the recent results of Doherty *et al.* cited above, by the dual receptor models.

Conclusions

That the genetic regulation of T lymphocyte function by the MHC has some clinical importance is indicated by the many associations between HLA antigens and disease susceptibility (Batchelor and Morris, 1977). Many of these associations are most strong with HLA DR antigens, which, as the human Ia antigens, suggests that Ir genes are involved. Examples are multiple sclerosis with HLA DRw2, rheumatoid arthritis with HLA DRw4, gluten enteropathy with HLA DRw3, and several other autoimmune diseases with HLA DRw3.

CTL may be implicated in diseases such as ankylosing spondylitis, where the association is with an HLA A or B antigen. One might expect to see strong associations with infectious diseases but data are generally lacking. There are two possible explanations for this. Firstly, that surveys so far have investigated association with *susceptibility* and not *resistance;* and, secondly, that in Western Europe and the United States, where studies have been done, exposure to pathogens is largely controlled by antibiotics, vaccination, and public health measures. Recent studies from tropical countries have begun to show association with major infectious diseases (de Vries *et al.*, 1976).

The idea that HLA antigens play a direct role in immunity to infectious diseases is very attractive because it gives a possible explanation for the extreme polymorphism and geographical variation found with this system (Bodmer, 1972; Piazza *et al.*, 1967). Disease epidemics, such as the influenza of 1918-9 which killed more than 20 million people (Kaplan and Webster, 1977), could have drastically altered the prevalence of HLA antigens in the

population by killing those that were genetically more susceptible.

The genetic restrictions placed on the immune response by the HLA system would thus have far-reaching consequencies. Genetic variability in the function of macrophages and B lymphocytes, although present, is less striking, perhaps because it is not antigen specific so that the range of variation compatible with survival is less.

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