INTRODUCTION

The autoimmune response is often an immune response that attacks one’s own tissues and causes disease. Most autoimmune diseases are organ-(tissue-) specific, and they develop when lymphocytes or their products (cytokines, antibodies, perforin, etc.) react with a limited number of antigens in that tissue. The molecular mechanisms leading to autoreactive immune responses resemble those generated against foreign antigens such as bacteria, parasites or viruses. However, in autoimmune disease either incomplete clonal deletion or formation of clonal anergy of T cells establishes a population of cells that is potentially intolerant but under special circumstances able to react with the host’s antigens. Autoimmune disorders are, then, characterized by the breaking of immunological tolerance or unresponsiveness to self antigens. This review focuses on evidence suggesting that some infectious agents, primarily viruses, can break immunologic tolerance and are implicated in autoimmune diseases. Discussed here are mechanisms by which this occurs and speculation on the use of such findings for understanding and treating human autoimmune disease.

WHAT EVIDENCE SUGGESTS THAT VIRUSES ARE IMPLICATED IN AUTOIMMUNITY AND AUTOIMMUNE DISEASES?

Newly forming autoimmune responses or those already present are enhanced after infection by a wide variety of human DNA and RNA viruses [1–5]. In fact, patients with immune responses to nucleic acids, cytoskeletal proteins, myosin and lymphocytes, etc. was publicized over 30 years ago by the great Swedish immunologist, Asterid Fagraeus. Additionally, experimental acute and persistent infections with DNA or RNA viruses have induced, accelerated or enhanced autoimmune responses and caused autoimmune disease [1]. The New Zealand mouse family is a genetically defined group in which certain strains spontaneously develop autoimmune disease. For example, among their several typical autoimmune responses, NZB mice develop antibodies to DNA and red blood cells, whereas NZB×NZW (F1 mice) develop antibodies to DNA and other nuclear antigens, closely resembling the picture of humans with systemic lupus erythematosus. When these mice are persistently infected with either a DNA (polyoma) or an RNA (lymphocytic choriomeningitis, LCMV) virus, their autoimmune responses occur earlier, reach higher titres and lead to disease sooner than in their uninfected counterparts. More interestingly, NZW mice, which normally do not develop autoimmune responses but contain the necessary gene(s) for autoimmune disease, develop these autoimmune responses after infection by polyoma virus or LCMV. Other viruses, including retroviruses, cause a similar phenomenon. In human autoimmune diseases like multiple sclerosis (MS), insulin dependent diabetes mellitus (IDDM) or ankylosing spondylitis, the incidence of disease varies in monozygotic twins suggesting that factors other than genetic and likely environmental also play a role [3–5]. It has been observed that infectious agents [6–8] or cytokines [9–12] released in the presence and/or absence of infections can break tolerance in potentially autoreactive CD4+ T or CD8+ T cells. Others have reported on epidemiologic and serologic correlations between certain viruses and autoimmune diseases like MS and IDDM. For example, Coxsackie B virus and rubella virus have been linked with IDDM [3, 13–15]. In a few instances, Coxsackie B virus has been directly isolated from pancreatic tissues of individuals with acute IDDM. Inoculation of this virus into mice then produced IDDM, fulfilling Koch’s postulates [16].

BY WHAT MEANS CAN VIRUSES INDUCE AUTOIMMUNE RESPONSES AND DISEASE?

A clue for a novel mechanism of virally elicited autoimmunity was found in the early 1980s. Observations at that time proved that monoclonal antibodies directed against a specific viral protein also cross-reacted with host self proteins [17–19]. For example, cross-reactivity was clear between measles virus phosphoprotein (72 kD molecular weight) and cytoskeletal keratin (54 kD molecular weight), and between herpes simplex virus glycoprotein (140 kD) and another epitope on keratin [18]. These observations received increased significance when the laboratories of Hilary Koprowski, Abner Notkins and ours established that roughly 5% of monoclonal antibodies made against 15 different kinds of viruses also reacted with host self determinants [2, 20]. These experiments analysed over 800 monoclonal antibodies against such commonly found representatives of DNA and RNA viruses as herpes simplex, cytomegalovirus, Epstein–Barr virus, vaccinia virus, myxoviruses, paramyxoviruses, arenaviruses, flaviviruses, orthoviruses, rhabdoviruses,
coronaviruses and human retroviruses. These results led to the hypothesis that molecules from dissimilar genes or their protein products shared structural similarities enabling them to mimic one another [18, 21]. The idea behind molecular mimicry is that the molecules’ linear amino acid sequences or their conformational fits are alike even though their origins are separate, for example, between a virus or a normal host self determinant. Cross-reactivity of this type from dissimilar proteins have been identified by assay of both humoral and cellular immune responses. Computer searches have also uncovered mimicry between host and viral proteins. Coupling this information with data on motifs of proteins (peptides) bound to MHC class I or class II proteins with outcomes from X-ray crystal-structure analysis has fine-tuned this hypothesis. For example, Wucherpfennig & Strominger [22] evaluated the cross-reactivity of known myelin basic protein (MBP)-reactive T cell clones derived from MS patients by using computer predicted peptides from a variety of viruses and bacteria. The results showed that peptides could be selected by predicting that their primary and secondary structures would fit into the HLA DR groove of major histocompatibility antigen complexes (MHC) molecules (the unique DR allele associated with MS). These authors then showed that the selected microbial peptides bound to and caused proliferation of clonally derived MBP reactive T cells with affinities either greater than or equivalent to the known MBP peptide. This outcome meant that a single T cell receptor could be activated by peptides from several different viruses including herpes simplex virus, Epstein–Barr virus, adenovirus and influenza A virus as well as one bacteria, Pseudomonas aeruginosa. Others showed that T cell lines established from MS patients reacted to MBP and also to the sequence from human respiratory coronavirus 229E [23]. Furthermore, molecular mimicry occurred between human transaldolase expressed selectively in oligodendrocytes, and human T cell lymphotropic virus, human immunodeficiency virus type 1, gag proteins [24, 25]. In other studies, cellular proliferative responses to determinants common to glutamic decarboxylase and Coxsackie B were noted [26]; a similarly shared proliferative response marked 25% of 16 newly diagnosed IDDM patients but none of 13 healthy matched control subjects [27]. These combined data indicate that molecular mimicry is not uncommon, is not restricted to any specific class or group of viruses, and clearly accompanies several autoimmune disease. An important addendum to these observations is the possibility that an immune response elicited against an infecting pathogen could or would eliminate it but could also cross-react with any self antigen that shares determinants with that pathogen. In this way, the immunopathologic process could continue chronically or be reinitiated by multiple viral infections. If so, disease continues after the determining agent has been eliminated, so its presence is no longer detectable, a ‘hit-and-run’ phenomenon [18, 21].

Several rules concerning the structure of peptides and their binding to MHC as well as the peptide-MHC complex binding the TCR are now established. Mutational and crystallographic studies of MHC molecules complexed with viral peptide show that the molecule’s flexible conformations allow peptides to bind within the MHC groove once their anchoring residues are fixed [22, 28, 29]. Analysis of residues flanking the anchoring residue(s) indicates the critical importance of minor pockets of MHC-binding clefts in peptide selectivity, leading to the concept that these structural factors are likely responsible for the preferential selection of specific peptides so often observed in interactions with MHC molecules [29–31]. This flexibility is biologically shown when a single TCR can cross-react with multiple ligands [22, 32, 33] including super antigens [34] and related self peptides [21, 22, 26, 35].

**EXPERIMENTAL EVIDENCE THAT MOLECULAR MIMICRY CAN ELICIT AUTOIMMUNE DISEASE**

A major component for the argument for the biological importance of molecular mimicry emanates from experiments with MBP and experimental allergic encephalomyelitis (EAE) in living animals [36]. For these experiments, MBP was selected as the host self component to test because its encephalitogenic site of 8–10 amino acids has been mapped in several animal species. Computer-assisted analysis showed significant homology between the encephalitogenic site of MBP and several viral proteins, but the best fit occurred between the MBP encephalitogenic site in the rabbit and hepatitis B virus polymerase. When this viral peptide was injected into rabbits, the histopathologic and immunologic hallmarks of EAE appeared (perivascular infiltration localized to the central nervous system; generation of lymphocytes that reacted (proliferated) to both rabbit MBP and the viral peptide). Other studies witnessed a similar scenario when the principle players were Coxsackie B3 or mouse cytomegalovirus infections, cardiac myosin and virus-induced myocardial disease [1, 37, 38]. These experimental models confirmed that molecular mimicry caused not only autoimmune responses but also autoimmune disease.

**THE PARAMETERS BY WHICH MOLECULAR MIMICRY IS ACTIVATED AND ASSOCIATED WITH VIRUS-INDUCED AUTOIMMUNE DISEASE**

To better understand the molecules and events involved in virus-induced autoimmune disease, we and others have designed transgenic mouse models [4, 6, 7, 39–41]. A cartoon of the model used for virus-induced IDDM and virus-induced oligodendrocyte autoimmune (demyelinating) disease is shown in Fig. 1. Our results from several studies based on the IDDM model [6, 9, 10, 12, 39] are reproduced in Fig. 2. For this model we used the rat insulin promoter (RIP) to express a viral gene in β cells of the islets of Langerhans. Diabetes does not occur spontaneously (incidence < 1% in these mice) unless tolerance is broken to the self (viral) antigen [6, 10, 39], in this situation the incidence of IDDM is 90–95%. When the transgene is expressed only in β cells, potentially autoreactive T cell clones of high
affinity pass through the thymus by positive selection and reside in the periphery [10, 39, 42]. These T cells are of high affinity. Upon challenge with the virus, IDDM follows within 7–12 days. However, the picture changes when the transgene is expressed in the target cell (β cells) and also in the thymus. In this instance, high affinity antiviral (self) T cells are removed by negative selection [10, 39, 42]. Passing to the periphery are low affinity T cells that are unresponsive (anergic). In the absence of viral infection, IDDM can be induced when such anergic CTL clones (of high or low affinity) in the periphery are activated as they pass into an islet environment where interferon-γ or B7.1 are expressed [9, 10]. In addition, activation of low affinity but not high affinity CTL clones requires CD4 help [39]. For IDDM to occur in both the high affinity and low affinity models, perforin [43, 44] and γ-interferon [12] are required. Experimentally disallowing γ-interferon expression [12] and/or establishing IL-4 expression in the islets [40] aborts the IDDM. Expression of γ-interferon [9] or TNF-α [45] in the islets quickens the kinetics and/or enhances the severity and incidence of IDDM.

These observations allowed us (von Herrath, Gairin, Horwitz, Sarvetnick & Oldstone) to design therapeutic approaches to halt the virus-induced IDDM [46–51]. When the cytokine profile in the islet of Langerhans milieu was changed from a Th1 to a Th2 phenotype (γ-interferon to IL-4, IL-10, TGFβ), IDDM was blocked [4, 5, 40, 46]. One interesting way this occurred was through the oral administration of porcine insulin [46, 49, 50]. This therapy had no demonstrable effect on precursor frequency.
of effector CD8<sup>+</sup> CTL. However, when a single or double amino acid change was made in the β chain of the insulin molecule that ordinarily protected against IDDM, the protective effect was lost and in some preparations IDDM was enhanced [49, 50]. In the latter instances, transgenic mice got IDDM within 1 week after LCMV challenge [49, 50]. This outcome documents how little we know about what controls immunity vs. tolerance with respect to oral therapy. A second approach was to design a peptide that bound at high affinity to the MHC allele involved in IDDM [47, 51]. By this means IDDM did not occur, CD4<sup>+</sup> and CD8<sup>+</sup> T cells were not placed in the islets but were found around them (peri-islets). A third approach was to abort expression of the MHC class I molecule by expressing the E3 transcription complex of adenovirus in β cells [48]. The focal reduction of MHC class I expression in the islets was associated with a normal precursor frequency of CD8<sup>+</sup> CTLs. Effector T cells were localized not in the islets but in the peri-islet positions and IDDM did not develop.

To examine whether molecular mimicry between a virus and a protein expressed in oligodendrocytes could lead to a central nervous system (CNS) autoimmune disease much like the demyelinating disease, multiple sclerosis, transgenic mice were generated whose oligodendrocytes expressed either the nucleoprotein or glycoprotein of a virus [41]. By this means IDDM did not occur, CD4<sup>+</sup> and CD8<sup>+</sup> T cells were not placed in the islets but were found around them (peri-islets). A third approach was to abort expression of the MHC class I molecule by expressing the E3 transcription complex of adenovirus in β cells [48]. The focal reduction of MHC class I expression in the islets was associated with a normal precursor frequency of CD8<sup>+</sup> CTLs. Effector T cells were localized not in the islets but in the peri-islet positions and IDDM did not develop.

To examine whether molecular mimicry between a virus and a protein expressed in oligodendrocytes could lead to a central nervous system (CNS) autoimmune disease much like the demyelinating disease, multiple sclerosis, transgenic mice were generated whose oligodendrocytes expressed either the nucleoprotein or glycoprotein of a virus [41]. Again, the viral transgene integrated into the germine and passed to progeny mice, it becomes a ‘‘self’’ antigen. Peripheral infection (initiated via intraperitoneal or intravenous routes) with a virus that encoded the same gene led to an antiviral immune response (predominantly CD8<sup>+</sup> CTL) that cleared the infection within 10 days, with entry and retention of activated antiviral (‘‘self’’) T cells (both CD8<sup>+</sup> and CD4<sup>+</sup> T lymphocytes) in the CNS and their retention along oligodendrocyte-produced myelinated tracts. Activation of microglia and enhancement of MHC class I and II expression paralleled the findings with T cells in the CNS [41] (Fig. 3). A more lasting effect, however, was chronic inflammatory disease of the CNS with activated T cells (both CD8<sup>+</sup> and CD4<sup>+</sup>) found in the white matter for over 1 year. A second infection with the initiating virus or an unrelated virus enhanced the CNS inflammation followed by loss of myelin associated with a clinical disorder of motor dysfunction (incoordination, weakness) (Fig. 3) [41]. Hence, a CNS autoimmune disease with myelin loss can be induced by infection with viruses that share epitopes with proteins expressed in oligodendrocytes, and this disease worsens after a second or multiple infections with the same or an unrelated virus. However, infection with the unrelated virus is, itself, unable to initiate the disease. Herein may lie an explanation for the clinical observations in MS patients [4, 5, 52, 53] of, first, the association of several different viruses with this autoimmune disease; second, the finding in their cerebral spinal fluids of antibodies to multiple viruses; and third, the epidemiologic pattern that exposure to an ‘‘environmental factor’’ early in life often predicts the later occurrence of such disease.

**CONCLUSIONS**

The concept of molecular mimicry is a viable hypothesis for framing questions and approaches in the investigation of the
aetiology, the pathogenesis, treatment and prevention of autoimmune disorders. Useful tools in this query are computer data banks, links between specific MHC alleles and particular autoimmune disease, identification of anchoring amino acids, and important flanking sequences that bind to the MHC allele or face to the T cell receptor within viral (microbial) peptides and information on the conformational fit. These tools now allow us to evaluate suspected microbial causes of autoimmune disorders and also self determinants that are likely contributors to the disease process. Transgenic models designed to evaluate molecular mimicry and virus-induced diseases reveal that unresponsive but potential autoimmune inducing T lymphocytes exist in the periphery. Such T lymphocytes, when activated by cytokines like interferon-γ or viral infection can act to break immune tolerance. Once activated, these lymphocytes release additional cytokines, the balance of which within the local milieu may determine whether autoimmune disease occurs rapidly, slowly, or not at all. After tissue damage begins, an autocatalytic reaction may follow during which other self antigens that cross-react with the infecting virus may participate. Specific therapies designed to inhibit viral replication, inactivate effector antiviral CD8+ CTL, or change the cytokine profile from a Th1 to Th2 have proven successful for treatment in these animal models and will likely, in the future, be adaptable to human autoimmune diseases.

ACKNOWLEDGMENTS

This is publication number 10732-NP from the Division of Virology, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, USA. This work was supported in part by USPHS grants AG04342, AI09484, and a grant from the Juvenile Diabetes Foundation (JDFI 995005). The author thanks Matthias von Herrath for input and assistance in the design of Figs 2 and 3.

REFERENCES

1 Oldstone MBA. Overview: Infectious agents as etiologic triggers of autoimmune disease. Curr Topics Microbiol Immunol 1989;145:1–3.
2 Oldstone MBA. Molecular mimicry as a mechanism for the cause and as a probe uncovering etiologic agent(s) of autoimmune disease. Curr Topics Microbiol Immunol 1989;145:127–35.
3 Notkins AL, Onodera T, Prabhakar B. Virus induced autoimmunity. In: Notkins AL, Oldstone MBA, eds. Concepts in Viral Pathogenesis. Heidelberg: Springer-Verlag, 1984:210–15.
4 von Herrath MG, Evans CF, Horwitz MS, Oldstone MBA. Using transgenic mouse models to dissect the pathogenesis of virus-induced autoimmune disorders of the islets of Langerhans and the central nervous system. Immunol Rev 1996;152:111–43.
5 von Herrath MG, Oldstone MBA. Virus-induced autoimmune disease. Curr Opin Immunol 1996;8:878–85.
6 Oldstone MBA, Nerenberg M, Southern P, Price J, Lewicki H. Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. Cell 1991;65:319–31.
7 Ohashi P, Oehen S, Buerki K et al. Ablation of tolerance and induction of diabetes by virus infection in viral antigen transgenic mice. Cell 1991;65:305–17.
8 Rocken M, Urban J, Shevach E. Infection breaks T-cell tolerance. Nature 1992;359:79–80.
9 Lee M-S, von Herrath M, Reiser H, Oldstone MBA, Sarvetnick N. Sensitization to self antigens by in situ expression of interferon-γ. J Clin Invest 1995;95:486–92.
10 von Herrath MG, Guerder S, Lewicki H, Flavell R, Oldstone MBA. Co-expression of B7.1 and viral (self) transgenes in pancreatic β-cells can break peripheral ignorance and lead to spontaneous autoimmune diabetes. Immunity 1995;3:727–38.
11 Ohashi P, Oehen S, Aichele P et al. Induction of diabetes is influenced by the infectious virus and local expression of MHC class I and TNF-α. J Immunol 1993;150:5185–94.
12 von Herrath MG, Oldstone MBA. Interferon-γ is essential for destruction of β cells and development of insulin-dependent diabetes mellitus. J Exp Med 1997;185:531–9.
13 Gamble DR, Taylor KW, Cumming H. Coxsackie viruses and diabetes mellitus. Brit Med J 1973;4:260–2.
14 Forrest JM, Menser MA, Burgess JA. High frequency of diabetes mellitus in young adults with congenital rubella. Lancet 1971;8:332.
15 Oldstone MBA, Notkins AL. Molecular mimicry. In: Notkins AL, Oldstone MBA, eds. Concepts in Viral Pathogenesis II. Springer-Verlag, New York, 1986:195–202.
16 Yoon J, Austin M, Onodera T, Notkins AL. Virus-induced diabetes mellitus. N Engl J Med 1979;300:1173.
17 Lane DP, Hoeffler WK. SV40 large T shares an antigenic determinant with a cellular protein of molecular weight 68,000. Nature 1980;288:167–70.
18 Fujinami RS, Oldstone MBA, Wroblewska Z, Frankel ME, Koprivski H. Molecular mimicry in virus infection: Cross-reaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments. Proc Natl Acad Sci USA 1983;80:2346–50.
19 Dales S, Fujinami RS, Oldstone MBA. Infection with vaccinia favors the selection of hybridomas synthesizing auto-antibodies against intermediate filaments, among them one cross-reacting with the virus hemagglutinin. J Immunol 1983;131:1546–53.
20 Srinivasappa J, Saegusa J, Prabhakar BS et al. Molecular mimicry: Frequency of reactivity of monoclonal antiviral antibodies with normal tissues. J Virol 1986;57:397–401.
21 Oldstone MBA. Molecular mimicry and autoimmune disease. Cell 1987;50:819–20.
22 Wucherpfennig KW, Strominger JL. Molecular mimicry in T-cell mediated autoimmunity: viral peptides activate human T-cell clones specific for myelin basic protein. Cell 1995;80:695–705.
23 Talbot PJ, Paquette J-S, Ciufri C, Antel JP, Ouellet F. Myelin basic protein and human coronavirus 229E: Cross-reactive T cells in multiple sclerosis. Ann Neurol 1986;39:233–40.
24 Banki K, Colombo E, Sia F et al. Oligodendrocyte-specific expression and autoantigenicity in transaldolase in multiple sclerosis. J Exp Med 1994;180:1649–63.
25 Colombo E, Banki K, Tatum AH et al. Comparative analysis of antibody and cell-mediated autoimmunity to transaldolase and myelin basic protein in patients with multiple sclerosis. J Clin Invest 1997;99:1238–50.
26 Tian J, Lehmann PV, Kaufman DL. T cell cross-reactivity between coxsackievirus and glutamate decarboxylase is associated with a murine diabetes susceptibility allele. J Exp Med 1994;180:1979–84.
Viruses and Autoimmune Diseases

27 Atkinson MK, Bowman MA, Campbell 1L, Darrow BL, Kaufman DL, Maclaren NK. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. J Clin Invest 1994;94:2125–9.

28 Bjorkman PJ, Saper MA, Samraoui B, Bennett WS, Strominger JL, Wiley DC. Structure of the human class I histocompatibility antigen, HLA-A2. Nature 1987;329:506–11.

29 Garcia KC, Degano M, Stanfield RL et al. The alphabeta T cell receptor structure at 2.5 A˚ and its orientation in the TCR-MHC complex. Science 1996;274:209–19.

30 Hedricher D, Mazarguil H, Laval F, Oldstone MBA, Gairin JE. Binding of viral antigens to major histocompatibility complex class I H-2Dα molecules is controlled by dominant negative elements at peptide non-anchor residues: Implications for peptide selection and presentation. J Biol Chem 1996;271:17829–36.

31 Sette A, Alexander J, Ruppert J et al. Antigen analogs/MHC complexes as specific T cell receptor antagonists. Ann Rev Immunol 1994;12:413–31.

32 Kersh GJ, Allen PM. Essential flexibility in the T-cell recognition of antigen. Nature 1996;380:495–8.

33 Tallquist MD, Yun TJ, Pease LR. A single T cell receptor recognizes structurally distinct MHC/peptide complexes with high specificity. J Exp Med 1996;184:1017–26.

34 Herman A, Kappler JW, Marrack P, Pullen AM. Superantigens: mechanism of T-cell stimulation and role in immune responses. Ann Rev Immunol 1991;9:745–72.

35 Evavold BD, Sloan-Lancaster J, Wilson KJ, Rothbard JB, Allen PM. Specific T cell recognition of minimally homologous peptides: evidence for multiple endogenous ligands. Immunity 1995;2:655–63.

36 Fujinama RS, Oldstone MBA. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 1985;230:1043–5.

37 Neu N, Rose NR, Beisel KW, Herskowitz A, Gurri-Glass G, Craig S. Cardiac myosin induces myocarditis in genetically predisposed mice. J Immunol 1997;158:3630–6.

38 O’Donoghue HL, Lawson CM, Reed WD. Autoantibodies to cardiac myosin in mouse cytomegalovirus myocarditis. Immunology 1990;71:20–8.

39 von Herrath M, Dockter J, Oldstone MBA. How virus induces a rapid or slow onset insulin-dependent diabetes mellitus in a transgenic mouse model. Immunity 1994;1:231–42.

40 Mueller R, von Herrath M, Oldstone MBA, Sarvetnick N. Expression of IL-4 in β cells of the islets of Langerhans aborts insulin dependent diabetes mellitus in a transgenic model. Manuscript submitted, 1997.

41 Evans CF, Horwitz MS, Hobbs MV, Oldstone MBA. Viral infection of transgenic mice expressing a viral protein in oligodendrocytes leads to chronic central nervous system autoimmune disease. J Exp Med 1996;184:2371–84.

42 von Herrath MG, Dockter J, Nerenberg M, Gairin JE, Oldstone MBA. Thymic selection and adaptability of cytotoxic T lymphocyte responses in transgenic mice expressing a viral protein in the thymus. J Exp Med 1994;180:1901–10.

43 Kagi D, Odermatt B, Ohashi PS, Zinkernagel RM, Hengartner H. Development of insulitis without diabetes in transgenic mice lacking perforin-dependent cytotoxicity. J Exp Med 1996;183:2143–52.

44 von Herrath M, Oldstone MBA. Molecules involved in β cell destruction. Submitted, 1997.

45 Ohashi PS, Oehen S, Aichele P et al. Induction of diabetes is influenced by the infectious virus and local expression of MHC class I and tumor necrosis factor-alpha. J Immunol 1993;150:5185–94.

46 von Herrath MG, Dyberg T, Oldstone MBA. Oral insulin treatment suppresses virus-induced antigen-specific destruction of β cells and prevents autoimmune diabetes in transgenic mice. J Clin Invest 1996;98:1327–31.

47 von Herrath MG, Coon B, Mazarguil H, Gairin JE, Oldstone MBA. A specific MHC class I restricted “blocking peptide” prevent activation of virus-induced CTL and the development of virus-induced autoimmune diabetes. J Exp Med 1997; submitted.

48 von Herrath MG, Efrat S, Oldstone MBA, Horwitz MS. Expression of adenooviral E3 transgenes in β-cells prevents autoimmune diabetes. PNAS 1997; in press.

49 Homann D, Dyberg T, Oldstone MBA, von Herrath M. A single amino acid change in the B-chain of insulin completely abrogates the efficacy of this compound to induce “oral tolerance” and prevent autoimmune diabetes. Manuscript submitted, 1997.

50 Homann D, Dyberg T, Oldstone MBA, von Herrath M. A single amino acid change in the B-chain of insulin completely abrogates the efficacy of this compound to induce “oral tolerance” and prevent autoimmune diabetes. Abstract: 21st Annual Conference of the La Jolla Immunologists, The Scripps Research Institute, La Jolla, CA, Nov. 7–8, 1996.

51 Gairin JE, Oldstone MBA. Design of high-affinity major histocompatibility complex-specific antagonist peptides that inhibit cytotoxic T-lymphocyte activity: Implications for control of viral disease. J Virol 1992;66:6755–62.

52 Ebers GC. Multiple sclerosis and other demyelinating diseases. In: Asbury, McKann, McDonald, eds. Diseases of the Nervous System. W.B. Saunders Co., Philadelphia. 1986:1268–81.

53 Kurtzke JE. Epidemiologic contributions to multiple sclerosis: An overview. Neurology 1986;30:61–79.