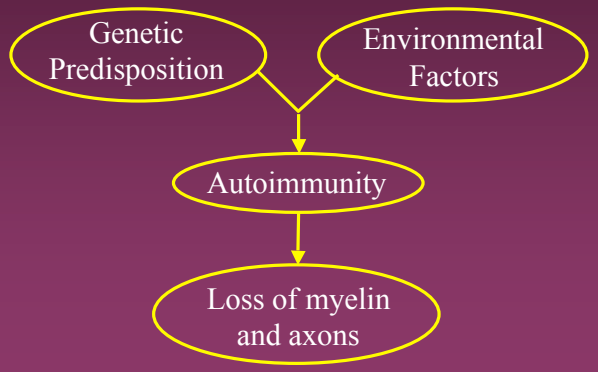
Immunopathogenesis of Multiple Sclerosis

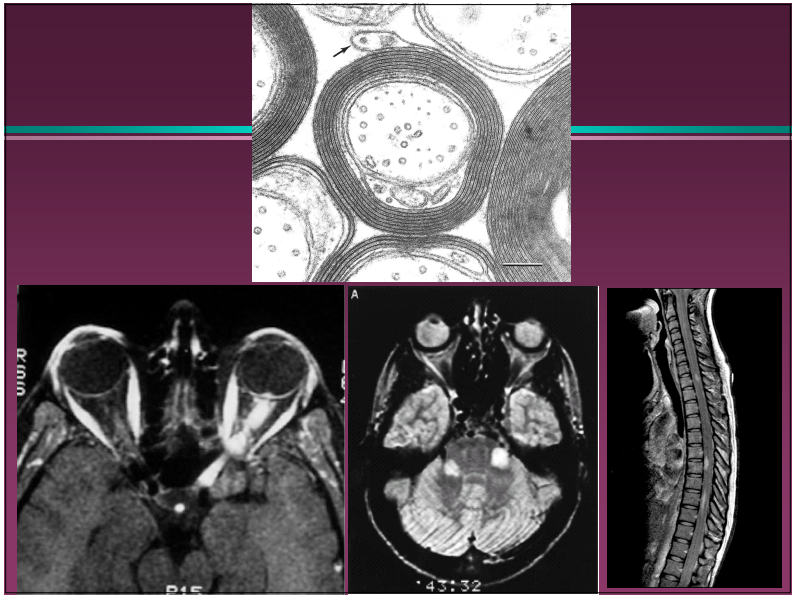
Epidemiology of MS

- Age of onset usually 20-40
- Higher prevalence in women
- 250,000-350,000 affected in U.S.
- Most common cause of nontraumatic disability in young adults
- National annual cost of MS $6.8-$11.9 billion

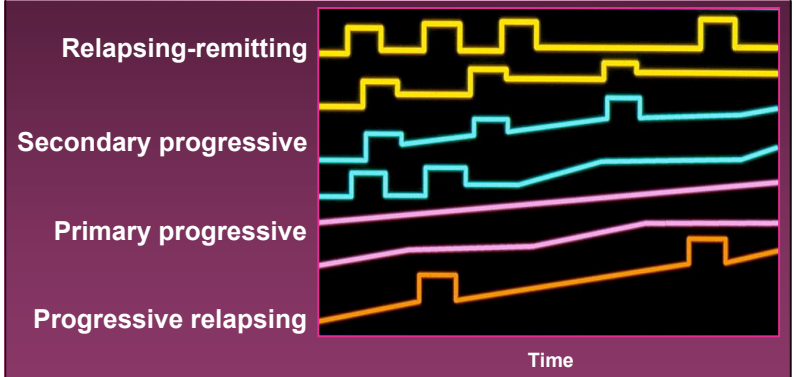
Whetten-Goldstein et al. *Mult Scler.* 1998;4:419-425

The Cause of MS is Unknown



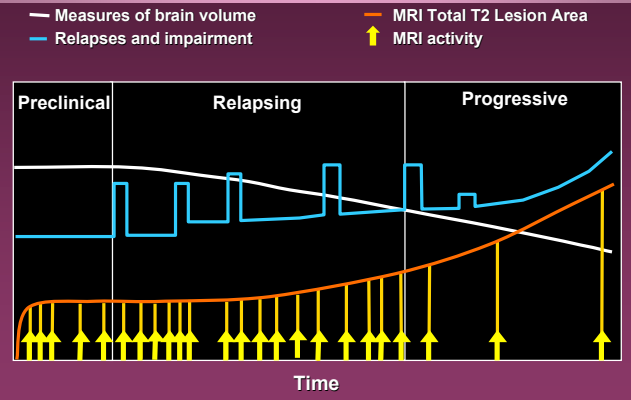


Clinical Patterns of MS



Adapted from Lublin et al. *Neurology*. 1996;46:907-911

Natural History of MS
Clinical and MRI Measures

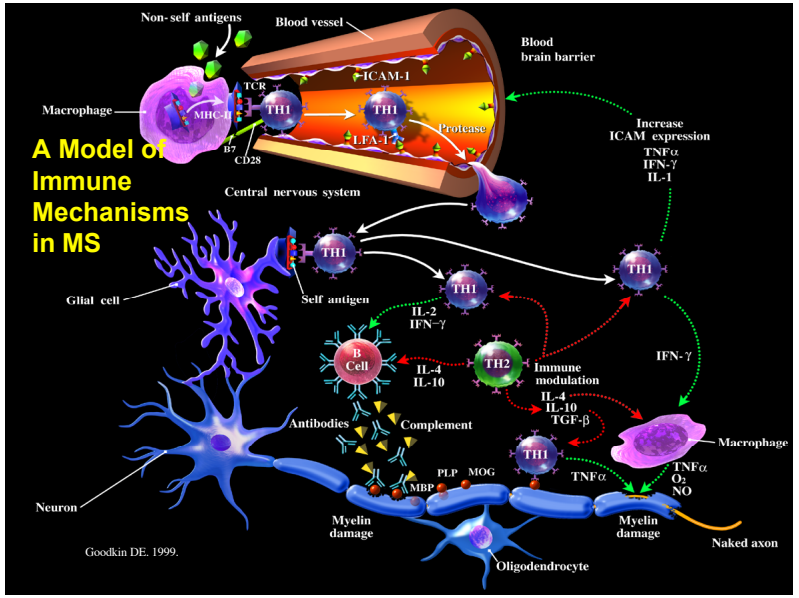


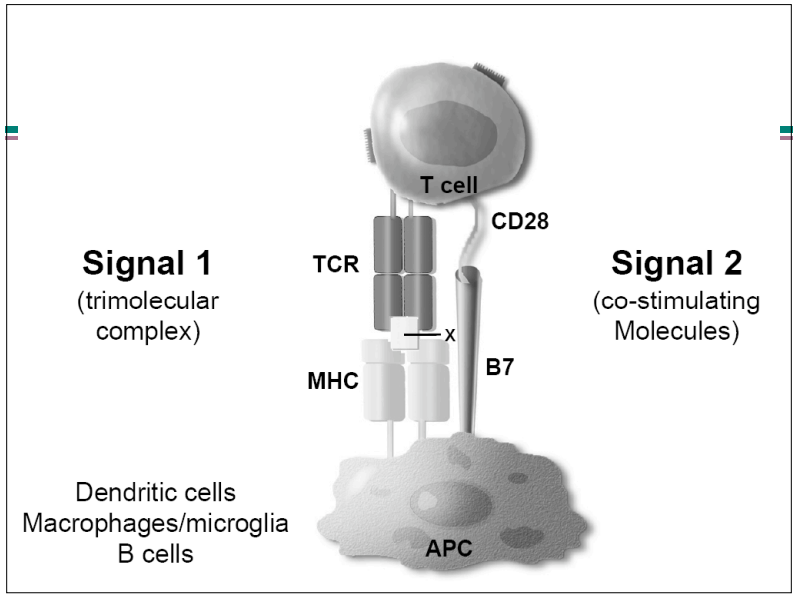
Hartung HP et al. *Lancet* 2002;360:2018-2025.

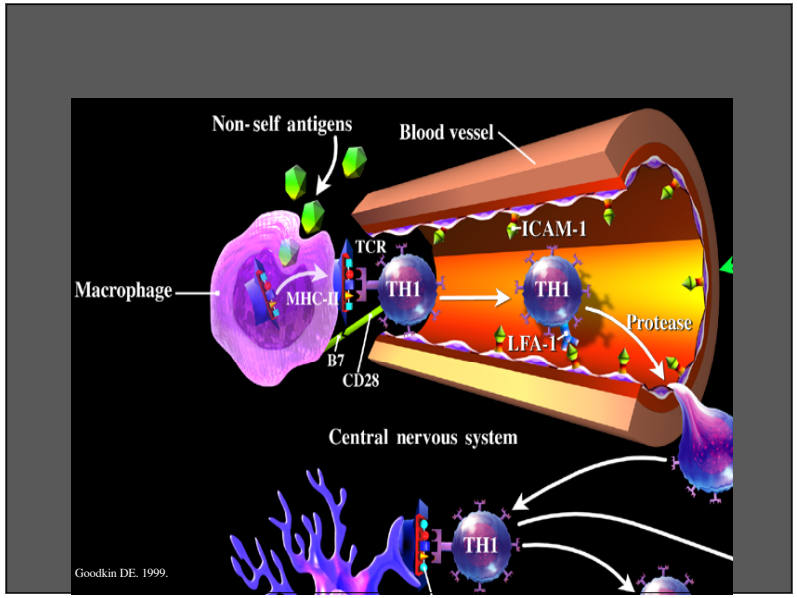
Neuropathologic Patterns of MS

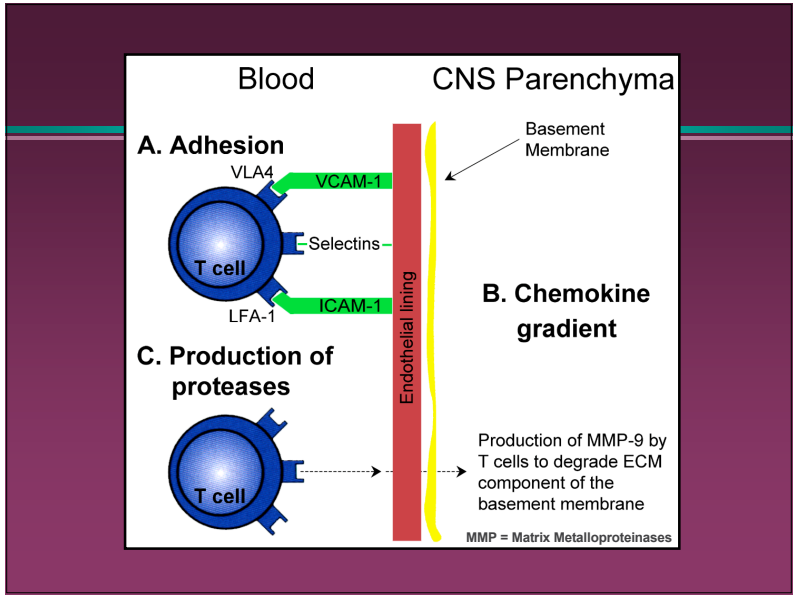
Pattern	I	II	III	IV
T Cells	**+++**	**++**	**++**	**++**
Macrophages	**++**	**++**	**++**	**+++**
Complement/ IgG	**-**	**++**	**-**	**-**
Demyelination	perivenous	perivenous	Non-perivenous; III defined	perivenous
Oligo loss	Variable	Variable	Pronounced	Pronounced
Oligo apoptosis	**-**	**-**	**++**	**-**
Remyelination	**++**	**++**	**-**	**-**
Frequency	3	1	2	4

Lucchinetti C, et al. *Ann Neur* 2000;407:707-17

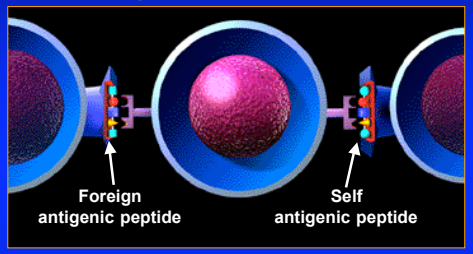



Signal 1
(trimolecular complex)
T cell
CD28
TCR
x
MHC
B7
APC
Signal 2
(co-stimulating Molecules)
Dendritic cells
Macrophages/microglia
B cells


Non-self antigens
Blood vessel
ICAM-1
TCR
Macrophage
MHC-II
TH1
TH1
Protease
LFA-1
B7
CD28
Central nervous system
TH1
Goodkin DE. 1999.



Molecular Mimicry: An Inability to Distinguish Non-self From Self

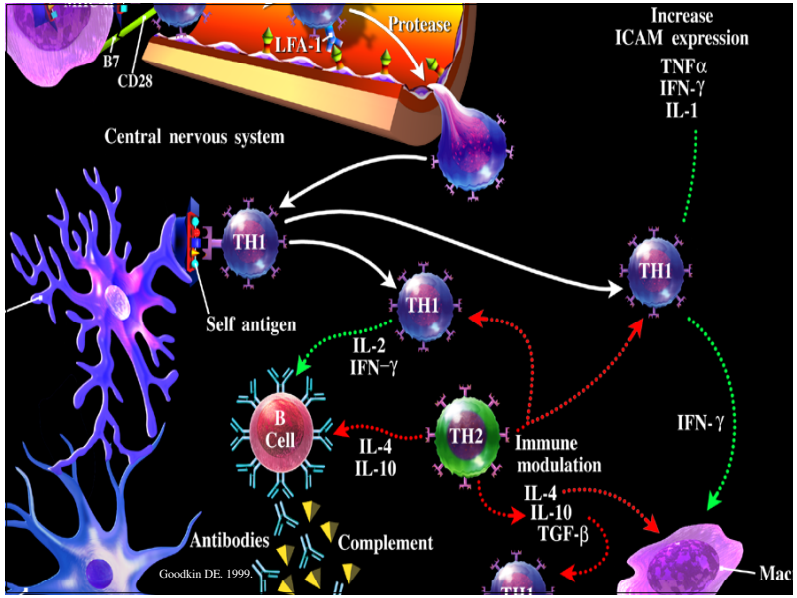


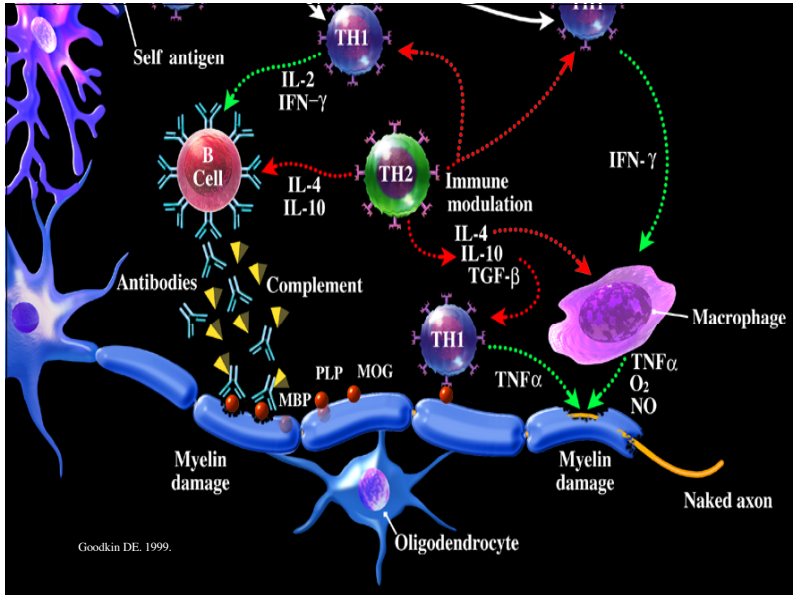
Potential Non-self Antigens

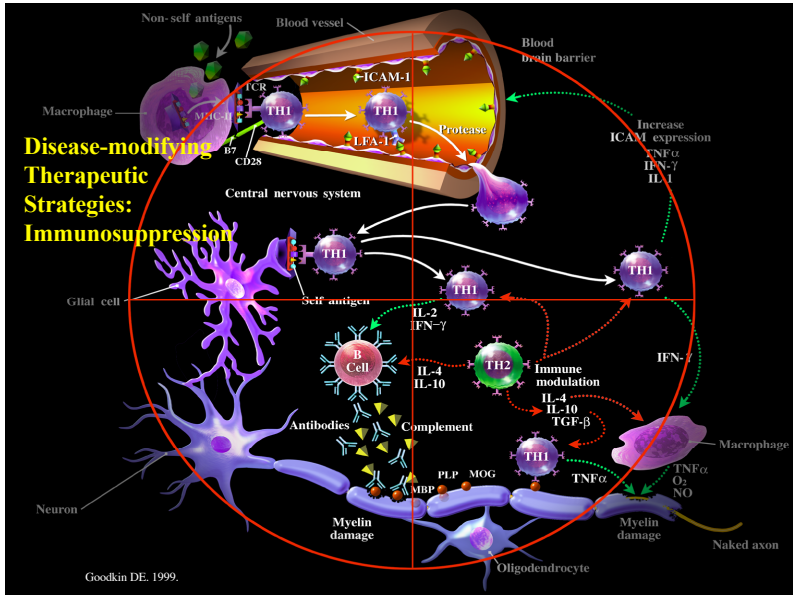
Viruses
Bacteria
Toxins

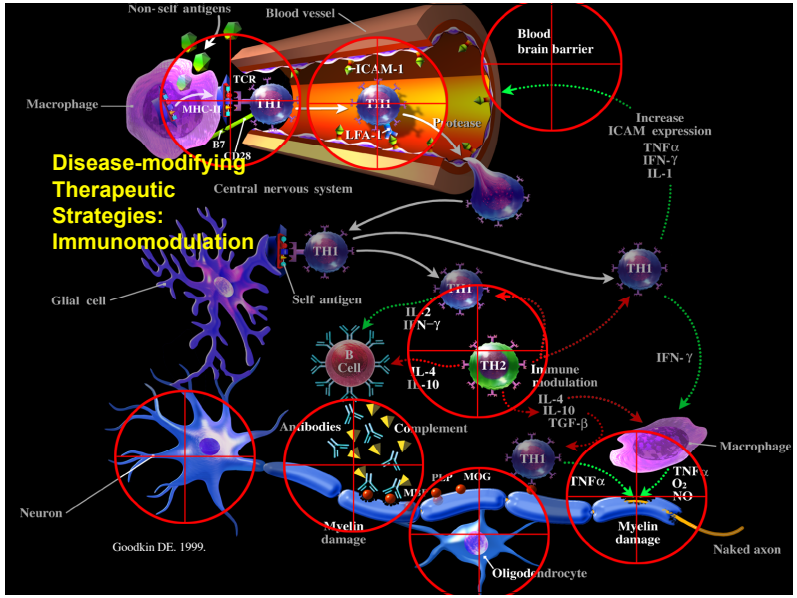
Potential Self Antigens

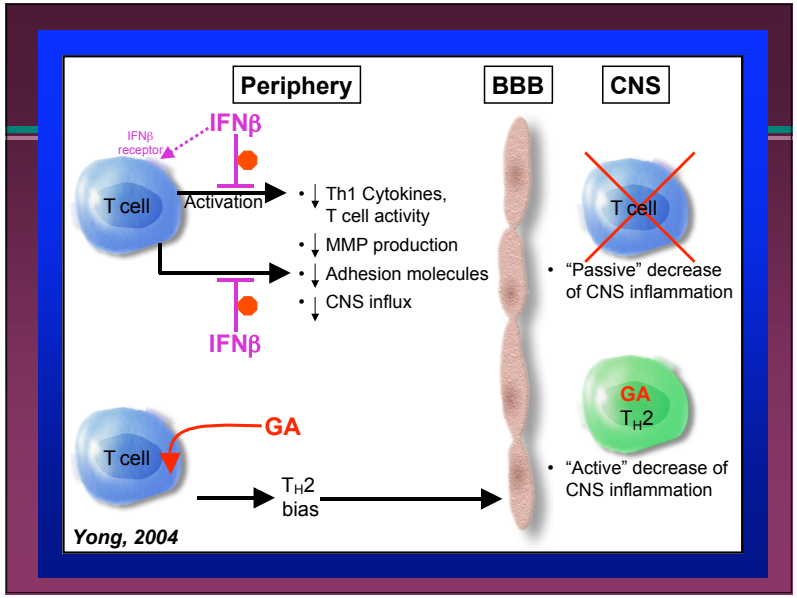
Myelin basic protein
Proteolipid protein
Myelin oligodendrocyte glycoprotein
Myelin associated glycoprotein

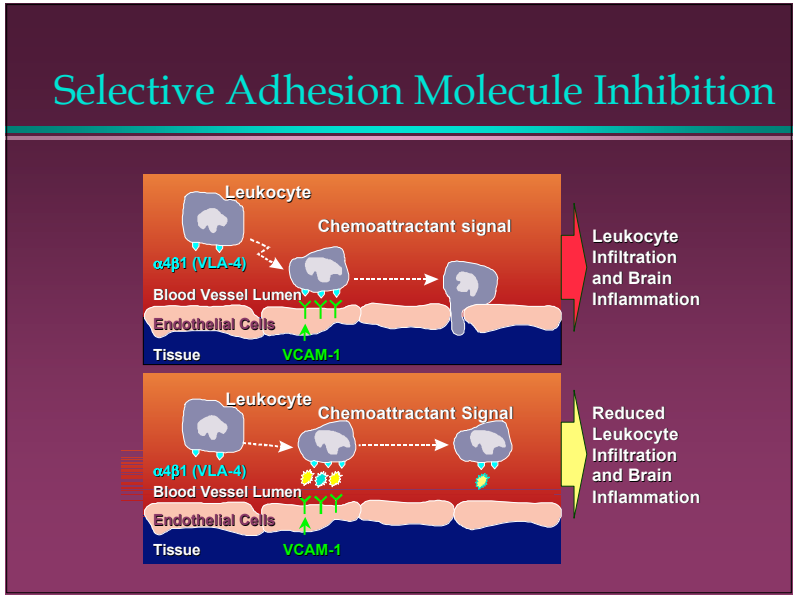

B7
CD28
LFA-1
Protease
Increase
ICAM expression
TNFα
IFN-γ
IL-1
Central nervous system
TH1
TH1
TH1
Self antigen
IL-2
IFN-γ
B
Cell
TH2
IL-4
IL-10
Immune
modulation
IFN-γ
IL-4
IL-10
TGF-β
Antibodies
Complement
Mac
Goodkin DE. 1999.

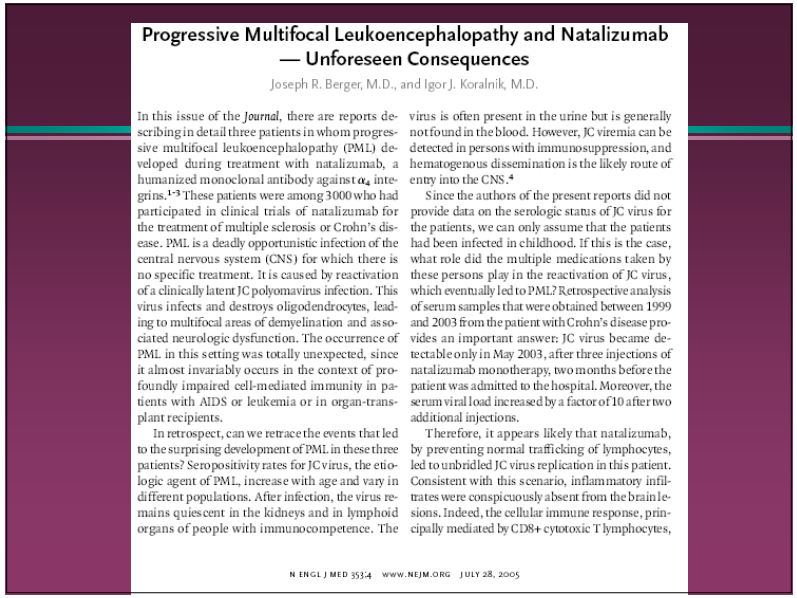

Self antigen
TH1
IL-2
IFN-γ
B
Cell
IL-4
IL-10
TH2
Immune
modulation
IFN-γ
IL-4
IL-10
TGF-β
Antibodies
Complement
Macrophage
TH1
PLP
MOG
MBP
TNFα
TNFα
O2
NO
Myelin
damage
Myelin
damage
Naked axon
Oligodendrocyte
Goodkin DE. 1999.


Disease-modifying Therapeutic Strategies: Immunosuppression
Non-self antigens
Blood vessel
Blood brain barrier
Macrophage
TCR
MHC-II
TH1
ICAM-1
LFA-1
Protease
B7
CD28
Increase ICAM expression
TNFα
IFN-γ
IL-1
Central nervous system
Glial cell
Self antigen
IL-2
IFN-γ
B Cell
TH2
IL-4
IL-10
Immune modulation
IL-4
IL-10
TGF-β
IFN-γ
Antibodies
Complement
PLP
MOG
MBP
TNFα
O2
NO
Neuron
Myelin damage
Oligodendrocyte
Naked axon
Goodkin DE. 1999.


Disease-modifying Therapeutic Strategies: Immunomodulation
Non-self antigens
Blood vessel
Blood brain barrier
Macrophage
TCR
MHC-II
TH1
ICAM-1
LFA-1
Protease
B7
CD28
Increase ICAM expression
TNFα
IFN-γ
IL-1
Central nervous system
Glial cell
Self antigen
IL-2
IFN-γ
B Cell
TH2
IL-4
IL-10
Immune modulation
IL-4
IL-10
TGF-β
IFN-γ
Antibodies
Complement
PLP
MOG
TNFα
O2
NO
Neuron
Myelin damage
Oligodendrocyte
Naked axon
Goodkin DE. 1999.


Periphery
BBB
CNS
IFNβ
IFNβ receptor
T cell
Activation
• ↓ Th1 Cytokines, T cell activity
• ↓ MMP production
• ↓ Adhesion molecules
• ↓ CNS influx
IFNβ
T cell
• "Passive" decrease of CNS inflammation
GA
T cell
GA
T_H2
T_H2 bias
• "Active" decrease of CNS inflammation
Yong, 2004


Selective Adhesion Molecule Inhibition
Leukocyte
Chemoattractant signal
α4β1 (VLA-4)
Blood Vessel Lumen
Endothelial Cells
Tissue
VCAM-1
Leukocyte Infiltration and Brain Inflammation
Leukocyte
Chemoattractant Signal
α4β1 (VLA-4)
Blood Vessel Lumen
Endothelial Cells
Tissue
VCAM-1
Reduced Leukocyte Infiltration and Brain Inflammation



Progressive Multifocal Leukoencephalopathy and Natalizumab — Unforeseen Consequences

Joseph R. Berger, M.D., and Igor J. Koralnik, M.D.

In this issue of the *Journal*, there are reports describing in detail three patients in whom progressive multifocal leukoencephalopathy (PML) developed during treatment with natalizumab, a humanized monoclonal antibody against α_4 integrins.[1-3] These patients were among 3000 who had participated in clinical trials of natalizumab for the treatment of multiple sclerosis or Crohn's disease. PML is a deadly opportunistic infection of the central nervous system (CNS) for which there is no specific treatment. It is caused by reactivation of a clinically latent JC polyomavirus infection. This virus infects and destroys oligodendrocytes, leading to multifocal areas of demyelination and associated neurologic dysfunction. The occurrence of PML in this setting was totally unexpected, since it almost invariably occurs in the context of profoundly impaired cell-mediated immunity in patients with AIDS or leukemia or in organ-transplant recipients.

In retrospect, can we retrace the events that led to the surprising development of PML in these three patients? Seropositivity rates for JC virus, the etiologic agent of PML, increase with age and vary in different populations. After infection, the virus remains quiescent in the kidneys and in lymphoid organs of people with immunocompetence. The virus is often present in the urine but is generally not found in the blood. However, JC viremia can be detected in persons with immunosuppression, and hematogenous dissemination is the likely route of entry into the CNS.[4]

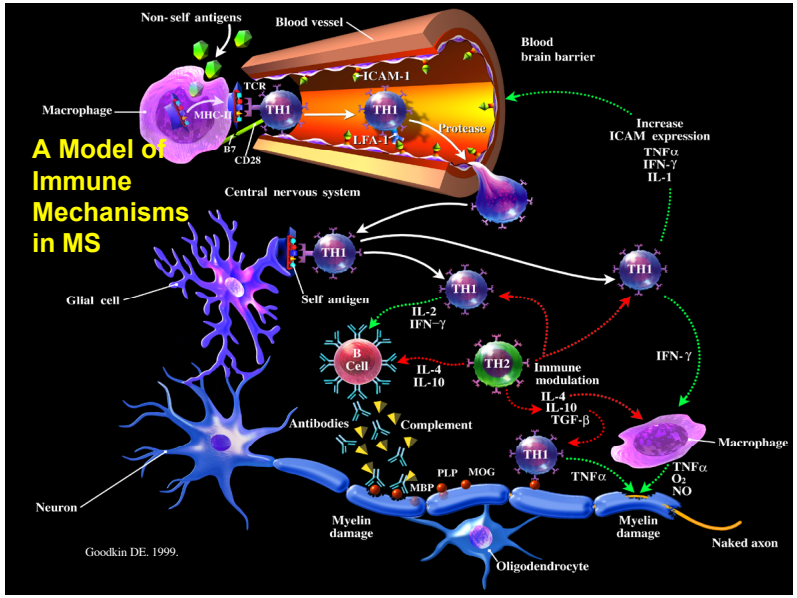
Since the authors of the present reports did not provide data on the serologic status of JC virus for the patients, we can only assume that the patients had been infected in childhood. If this is the case, what role did the multiple medications taken by these persons play in the reactivation of JC virus, which eventually led to PML? Retrospective analysis of serum samples that were obtained between 1999 and 2003 from the patient with Crohn's disease provides an important answer: JC virus became detectable only in May 2003, after three injections of natalizumab monotherapy, two months before the patient was admitted to the hospital. Moreover, the serum viral load increased by a factor of 10 after two additional injections.

Therefore, it appears likely that natalizumab, by preventing normal trafficking of lymphocytes, led to unbridled JC virus replication in this patient. Consistent with this scenario, inflammatory infiltrates were conspicuously absent from the brain lesions. Indeed, the cellular immune response, principally mediated by CD8+ cytotoxic T lymphocytes,

N ENGL J MED 353;4 www.NEJM.ORG JULY 28, 2005

Evidence that MS may not be a Th1-mediated disease

- IL-12 receptor deficient mice are suseptible to EAE
- Treatment with IFN-γ and anti TNF-α worsens MS
- Th1 $\rightarrow$ Th2 only results in a modest treatment effect
- In some MS lesions the majority of clonally expanded lesions are CD8+
- IL-23, which may be involved in expansion and maintaining the population of Th17 cells, is found in MS lesions
- MS may be a primary neurodegenerative disease in some patients



Type 1 Diabetes

- An autoimmune disease involving systematic and specific destruction of pancreatic islet beta cells
- Multiple genetic contributions
- Possible environmental trigger
- Long latent period
- Incidence appears to be increasing worldwide – accounts for 5-10% of all diabetes
- May appear in adulthood (LADA)

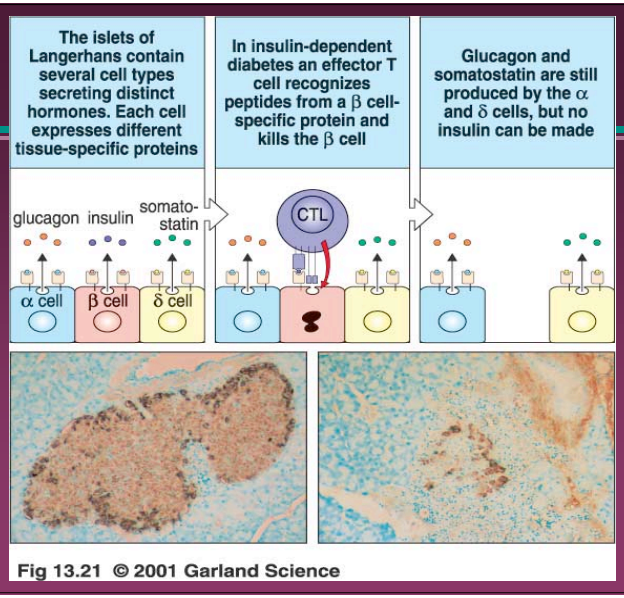


Fig 13.21 © 2001 Garland Science

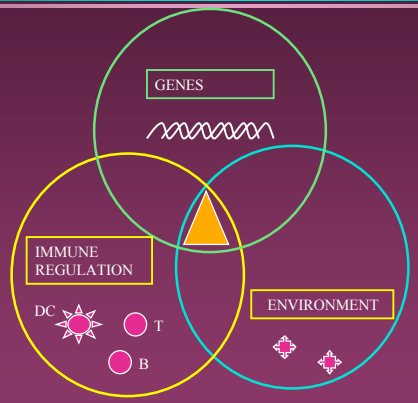
Islet autoantigens

- GAD 65
- insulin
- IA-2 (protein tyrosine phosphatase of unknown function)
- proinsulin
- carboxypeptidase H
- peripherin
- IGRP (CD8 antigen)

Diagnostic sensitivity and specificity of autoantibodies for type 1 diabetes

Autoantigen	Sensitivity, %	Specificity, %
Insulin	40-70	99
GAD65	70-80	99
IA-2	50-70	99

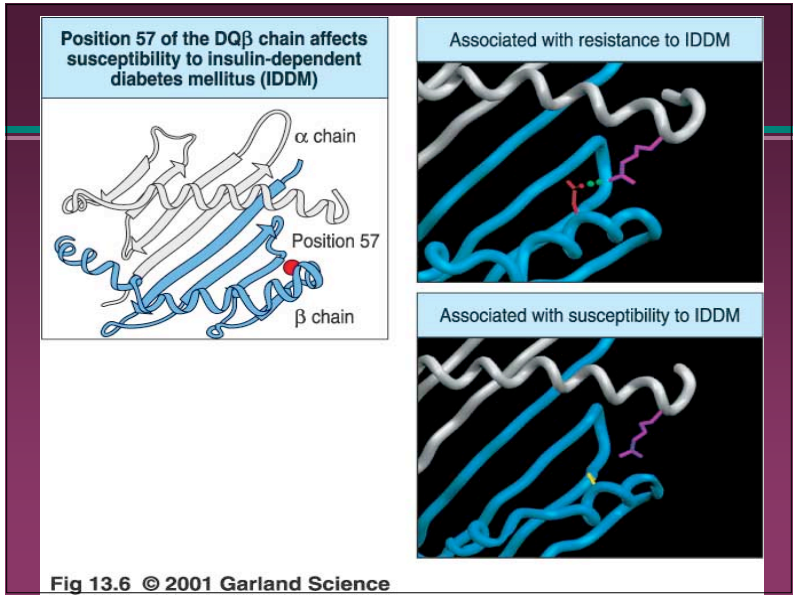
Autoimmunity



Adapted from Fathman Nat Immunol:9:760 2001

Genetics of Type 1 diabetes

- monozygotic twins have a 30-50% concordance rate
- HLA identical siblings have a 10-25% concordance rate
- The most susceptible HLA type is associated with 5% risk
- DQ beta 0302 and 0201 susceptible
- DR2 and DQ beta 0602 protect
- 30% also have AIT, 4-9% have Celiac disease and 0.5% have Addison's disease
- Increased rate of autoimmunity in relatives



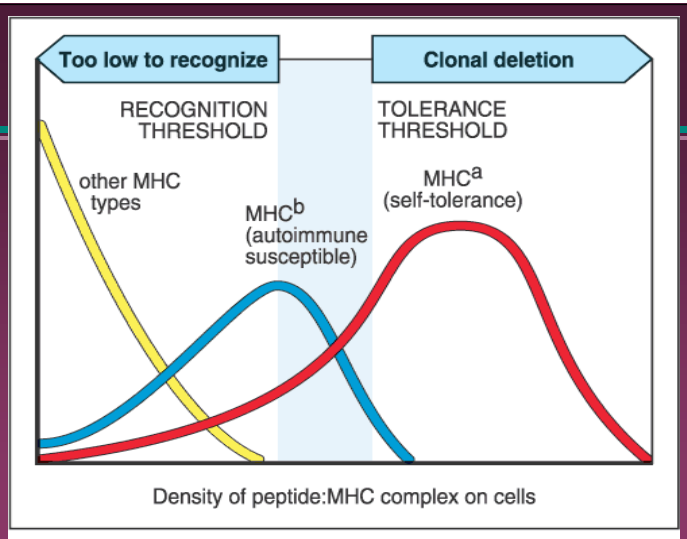


Fig 13.33 © 2001 Garland Science

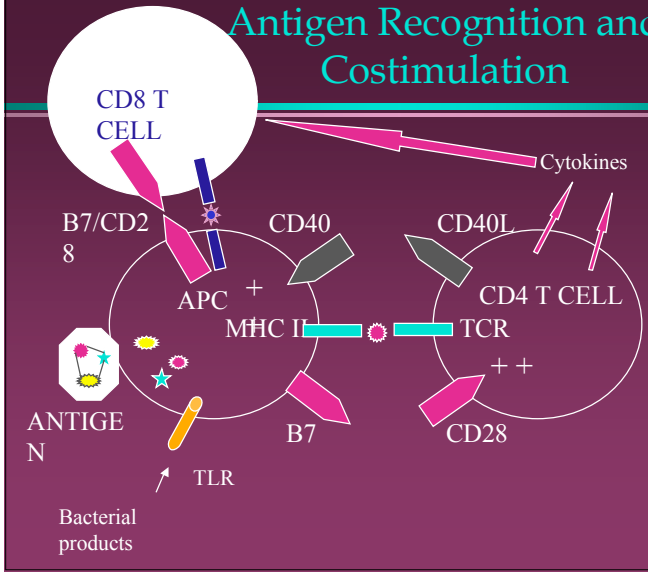
Genetics of Type 1 diabetes - other candidate loci (16-20)

- insulin
  - » level of expression may influence thymic selection
- CTLA4
  - » controls T cell regulation
- PTPN22 (lymphoid tyrosine phosphatase)
- Others
  - » MIC-A
  - » TGF-β
  - » zfp36 (controls TNF-α production)
  - » IL-1
  - » sle3

Mechanism

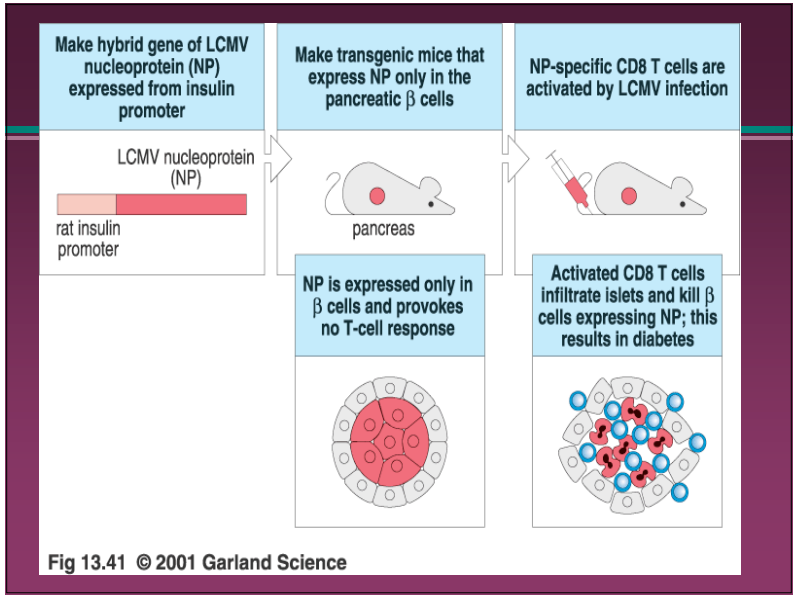
- Unknown trigger activates diabetogenic T cells that recognize islet cell antigens
  - » early islet infiltration by APC's and T cells
  - » B cells may be key APC's
- Both CD4 and CD8 cells are required for initiation of disease
  - » effector cells are CD8
- Th1 type cytokines are involved
- Rate of progression is variable

Antigen Recognition and Costimulation



What triggers disease?

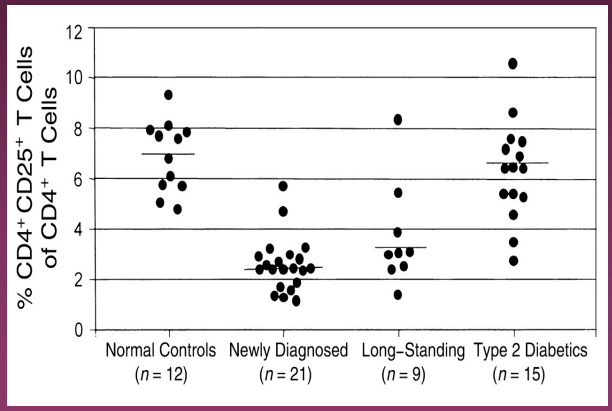
- Self antigen
- Microbial antigen
- Molecular mimicry
- Local inflammation



Regulation of diabetes

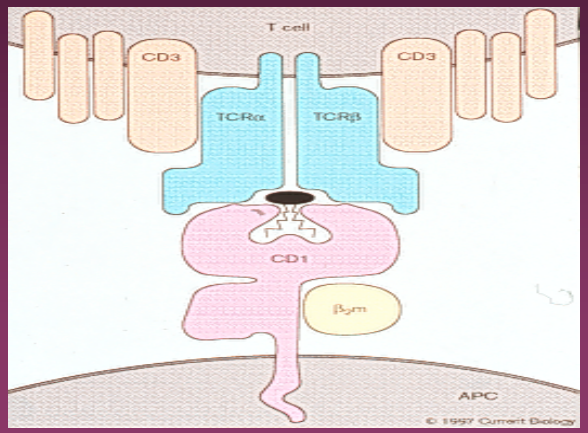
- Progression is regulated by at least two known subsets of T cells
  - » CD4/CD25+ T cells
  - » NK1.1 (Vα24/Vβ11) T cells
    - – Genetically regulated

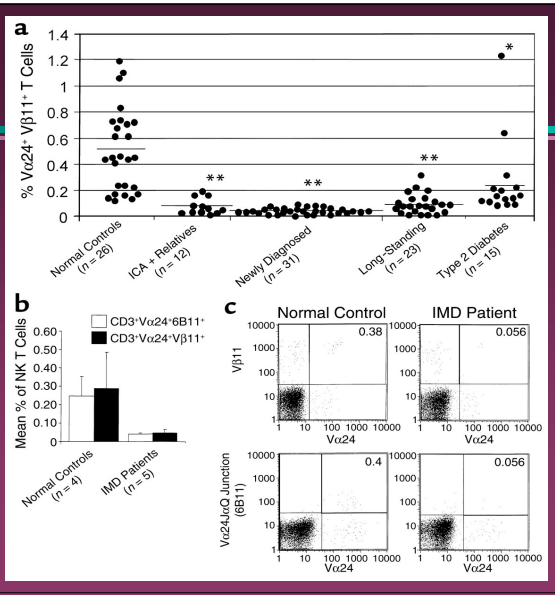
Newly diagnosed diabetics have defects in CD4/CD25 regulatory cells



Kukreja et al. J. Clin. Invest. 109:131 2002

CD1 recognizes lipid antigens presented by NK1.1 T cells



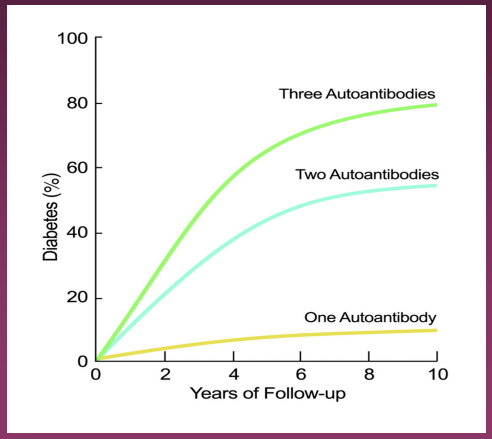


Kukreja et al. J. Clin. Invest. 109:131 2002

THE PATIENT AT RISK

- FAMILY HISTORY
- > 2 ANTIBODIES
- SUSCEPTIBLE HLA (2.4% newborns)
  - » ? ABNORMAL CYTOKINE SECRETION
  - » LOSS OF REGULATORY T CELL POPULATIONS
  - » OTHER GENETIC MARKERS

The number of autoantibodies predicts risk in relatives



Notkins and Lernmark

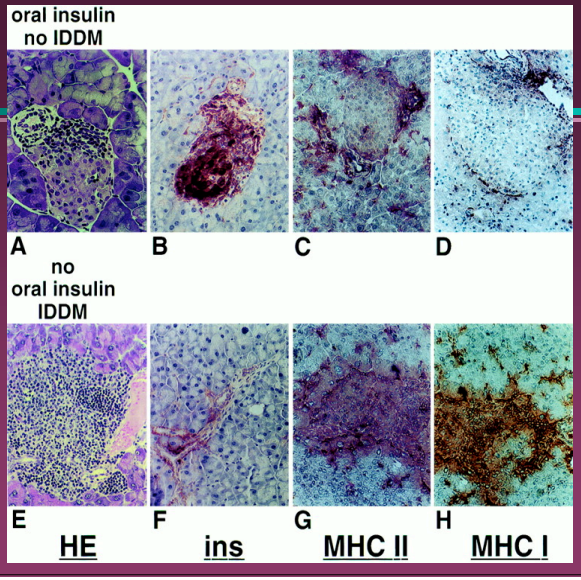
J. Clin. Invest 108:1247 2001

Preclinical course of diabetes

- Autoantibodies present
- Abnormal first phase insulin response following IV glucose challenge
- Impaired GTT
- Abnormal fasting glucose
- Loss of C-peptide
- Testing for autoreactive T cells not available yet in humans

Diabetes prevention

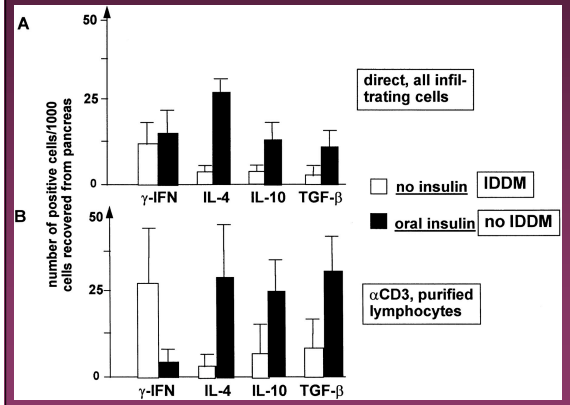
- Before the onset of autoantibodies
  - » Remove environmental triggers (?cows milk)
  - » Transcriptional regulation of key antigens
- After the onset of autoantibodies
  - » Immune suppression
  - » Tolerance induction (switch to Th2 response)
  - » Induction of regulatory T cells



Von Herrath et al

J Clin Invest 1996 98:1324-31

Oral insulin prevents diabetes in mice by immune deviation



Von Herrath et al

J Clin Invest 1996 98:1324-31

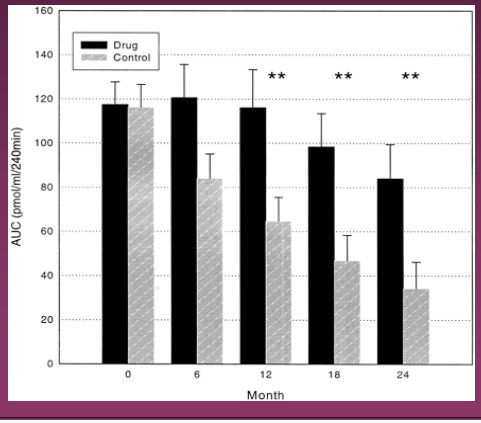
The Diabetets Prevention Trial (DPT-1)

- Focused on insulin as tolerogenic agent
- Both i.v. and oral arms in patients at risk (700 individuals)
- Neither arm worked (used too late?)
- Stresses the differences between prevention, initiation and effector phases of disease
- A GAD trial is underway

Anti-CD3 prevents diabetes in mice and delays onset in humans

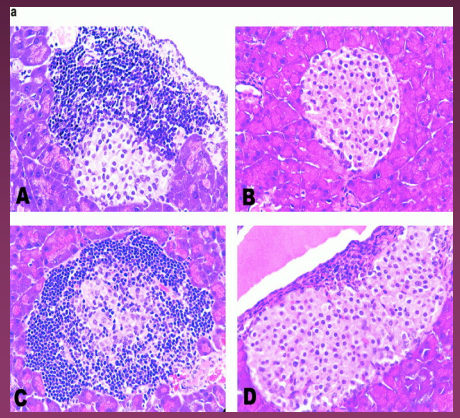
- Non-depleting anti-CD3 antibody
- Dos not induce a cytokine storm
- A single dose resulted in delay in disease onset for up to two years (42 patients)
- Delivery with nasal antigen induced Tregs in a mouse model

Prevention of loss of C peptide after anti-CD3 treatment



Herold et al Diabetes 54:1763-1769, 2005

Reversal of insulitis by LTN-β receptor antagonist



Wu et al

J Exp Med 2001 193:1327-32

Islet transplant

- Edmonton protocol
  - » Steroid free
  - » Anti-CD25
  - » Sirolimus and tacrolimus
  - » Large transplant mass delivered to portal vein
  - » Meticulous tissue preparation and transport
  - » ? Addition of anti-apoptotic or anti-inflammatory regimens
  - » No good markers for rejection
  - » Requires longterm immunosuppression

THE PRESENT

- TREAT KETOACIDOSIS
- START INSULIN
- CONTINUE FOR LIFE
- TREAT COMPLICATIONS
  - » CARDIO AND PERIPHERAL VASCULAR
  - » RENAL
  - » OCULAR

THE FUTURE

- PREVENT DISEASE IN PATIENTS AT RISK
  - » Identify by HLA TYPING + ANTIBODIES
- IMMUNE MODULATION
  - » Cyclosporine A
  - » other immunosuppressives
  - » Biologic reagents (which?)
- PREVENTION BY induction of tolerance
- RESTORATION OF REGULATORY CELLS
- RESTORATION OF islet cells