

## Autoimmunity in Man

Autoimmune diseases are MHC-linked

MHC genes are immune response genes  
Indicates a role for T cells in these diseases

## How might autoimmunity emerge?

- Crossreactivity/Molecular Mimicry
- Inflammation (IFN- $\gamma$ ) induced Neo-expression of class II MHC and the presentation of novel MHC-peptide complexes to which the system is not tolerant
- Breaking tolerance by the induction of co-stimulator activity or by interfering with normal suppressor or regulatory mechanisms
- Imbalance of Th1/Th2 cells
- Not autoimmunity (really a viral or bacterial disease)

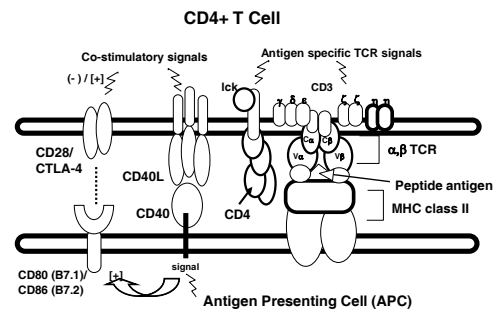
## Autoimmunity in Man

In most organ specific autoimmune syndromes, there is neo-class II MHC expression

IFN- $\gamma$  and TNF secreted during immune and inflammatory responses induces upregulation of class II MHC.

This permits presentation of new self antigens to the immune system

T cell activation is regulated by signals derived from the TCR /CD3/CD4 complex and the CD40L and CD28/CTLA-4 co-stimulatory molecules

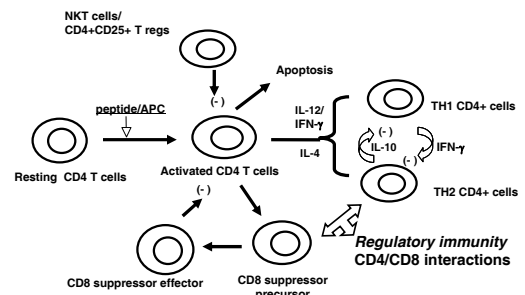


## Autoimmunity in Man

In most organ specific autoimmune syndromes, the T cell response is pauci-clonal

- T cells infiltrating the target organ use only a few related TCR genes
- Indicates that these diseases are due to particular peptide antigen(s) presented by MHC

## The Control of Activated CD4+ T Cells by Regulatory T cells



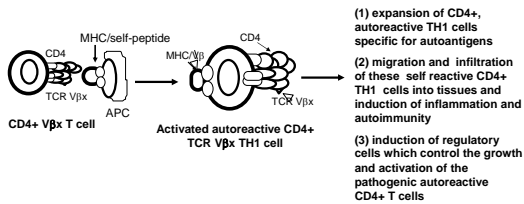
### Functions of Th1 and Th2 cells

Type	Function	Helpful	Harmful
Th1 ↓ IL-2 IFN-γ TNFα	Activate macrophages, dendritic cells  DTH	Tb, fungi, Leishmania and other intracellular bacteria	MS Thyroiditis RA IDDM Scleroderma poison ivy
Th2 ↓ IL-4 IL-5 IL-6 IL-10	B cell help  down-regulate Th1  class switching	Clearance of antigens/toxins Helminths	Allergy Autoantibody SLE

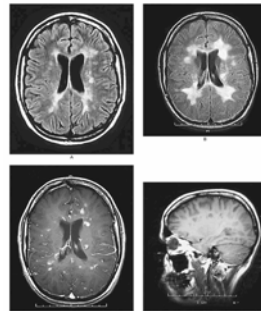
### Clinical Aspects of Multiple Sclerosis

- (1) The clinical symptoms of the disease are entirely attributable to immune-mediated injury of myelin and subsequent demyelination in the CNS.
- (2) Clinical problems may include disturbances in visual acuity and blindness; double vision; motor disturbances affecting walking and use of the hands; bowel and bladder incontinence; spasticity; and sensory disturbances including loss of touch, pain, and proprioception. Cognitive function is generally not impaired in MS.
- (3) A typical presentation of MS involves episodes of relapse followed by remission. Relapses often follow an episode of a viral infection of the upper respiratory system or gastrointestinal tract. In many MS cases the disease progresses to a more chronic phase.

### Induction of CD4+ TH1 mediated autoimmunity: A paradigm for the pathogenesis of rheumatoid arthritis, multiple sclerosis and type I diabetes



### MRI Scans of the Brain of a 25-Year-Old Woman with Relapsing-Remitting Multiple Sclerosis

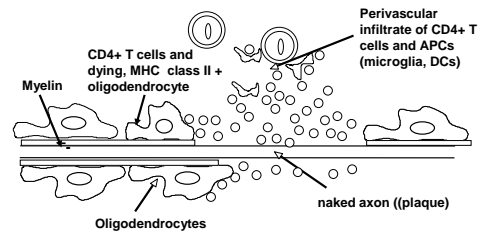


An axial MRI image shows multiple ovoid and confluent hyperintense lesions in the periventricular white matter (Panel A). Nine months later, the number and size of the lesions have substantially increased (Panel B). After the administration of gadolinium, many of the lesions demonstrate ring or peripheral enhancement, indicating the breakdown of the blood-brain barrier (Panel C). In Panel D, a parasagittal T1-weighted MRI scan shows multiple regions in which the signal is diminished (referred to as "black holes") in the periventricular white matter and corpus callosum. These regions correspond to the chronic lesions of multiple sclerosis.

### Multiple sclerosis (MS) Overview

- (1) Multiple sclerosis (MS) is the most common autoimmune disease involving the central nervous system (CNS). In the United States ~250,000 individuals suffer from MS.
- (2) The first clinical signs of MS typically begin in young adulthood, and women with the disease outnumber men 2:1. The cause of the disease is unknown, but genetic factors including MHC class II genes are important with HLA DR2 carrying a 4-fold relative risk for northern European caucasoids.
- (3) The pathology of the disease lies entirely in the central nervous system and is characterized by a classic picture of inflammation surrounding venules and extending into the myelin sheath.

### Immunopathology of MS



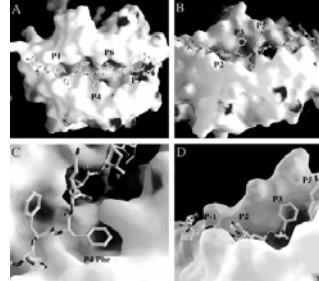
### Pathophysiology of MS: 1

(1) Genetic and environmental factors (including viral and bacterial infection) facilitate the movement of autoreactive T cells from the systemic circulation into the central nervous system (CNS) through disruption of the blood-brain barrier.

(2) In the CNS, local factors up-regulate the expression of endothelial adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin, further facilitating the entry of T cells into the CNS.

(3) Proinflammatory cytokines like IFN- $\gamma$  and TNF up-regulate the expression of surface MHC molecules on neighboring tissue and antigen-presenting cells. Binding and presentation of putative multiple sclerosis (MS) antigens, including myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP), to the TCR/MHC class II complex on APC's triggers an autoreactive immune response.

### Structure of the HLA-DR2-Myelin Basic Protein (MBP) peptide complex



Top and side view of the HLA-DR2-MBP peptide complex. 14 residues are included for the MBP peptide (P-3 Asn to P11 Arg). P1 Val and P4 Phe occupy the hydrophobic P1 and P4 pockets, respectively, and serve as primary anchor residues of the MBP peptide. (C) View of the large P4 pocket of HLA-DR2 occupied by P4 Phe of the MBP peptide. Gln 70 is positioned over P4 Phe of the peptide. (D) TCR contact residues of the MBP peptide. P2 His, P3 Phe, and P5 Lys that were previously shown to be important for TCR recognition of the MBP peptide (Wucherpfennig, K. J. Exp. Med: 188, 1511, 1998)

### Pathophysiology of MS: 2

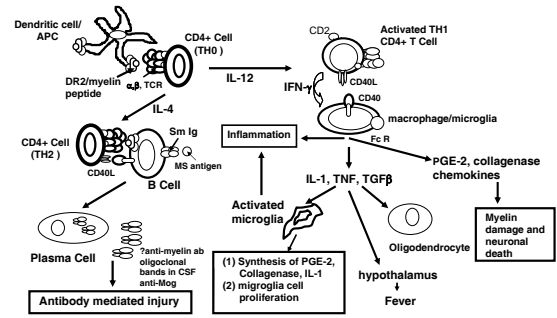
(4) Proinflammatory cytokines (e.g., interleukin-12) trigger a cascade of events, resulting in the proliferation of proinflammatory CD4+ Th1 cells, release of IFN- $\gamma$ , activation of macrophages and ultimately in immune-mediated injury to myelin and oligodendrocytes.

(5) Multiple mechanisms of immune-mediated injury of myelin have been postulated: cytokine-mediated injury of oligodendrocytes and myelin; direct injury of oligodendrocytes by CD4+ and CD8+ T cells; antibody-dependent cytotoxicity and complement-mediated injury; phagocytosis by macrophages

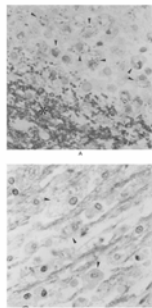
(6) This injury to the myelin membrane results in denuded axons that are no longer able to transmit action potentials efficiently within the central nervous system resulting in neurologic symptoms.

(7) This TH1 mediated injury may be controlled both by cytokines released from Th2 T cells or alternatively by regulatory CD4+ or CD8+ T cells which down regulate the Th1 response.

### Immunopathophysiology of Multiple Sclerosis



### Photomicrographs of an Actively Demyelinating Multiple Sclerosis Lesion



(Immunocytochemical Staining of Myelin Oligodendrocyte Glycoprotein [Brown] with Hematoxylin Counterstaining of Nuclei [Blue]). In Panel A, at the active edge of a multiple sclerosis lesion (indicated by the asterisk), the products of myelin degradation are present in numerous macrophages (arrowheads) (x100). In Panel B (x100), macrophages containing myelin debris (arrowheads) are interdigitated with degenerating myelin sheaths.

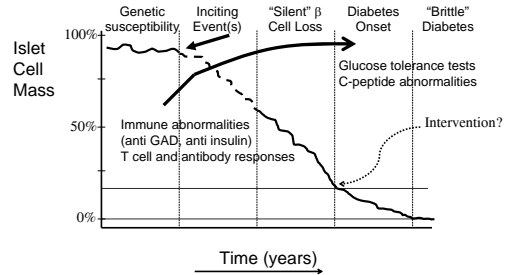
### Overview of insulin dependent diabetes mellitus (IDDM)

- IDDM is an autoimmune disease that affects 0.3% of the world's population. In the United States, the prevalence of IDDM by the age of 20 years is about 0.26 percent, and the lifetime prevalence approaches 0.4 percent.
- IDDM is mediated by autoaggressive CD4+ and CD8+ T cells that infiltrate the pancreas, induce islet  $\beta$  cell insulinitis eventually leading to death or damage to the insulin-producing  $\beta$ -islet cells.
- The cause of the disease is unknown, but genetic factors including HLA class II genes exert an influence manifest as a complex interplay between alleles of the two major MHC class II molecules, HLA DR and DQ. In particular, particular alleles of DR3, DR4 and DQ2 and DQ8 confer the highest risk for IDDM.

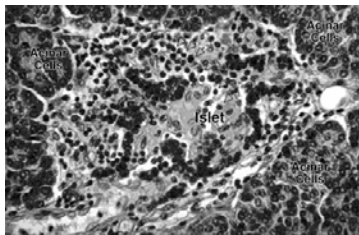
### Overview of insulin dependent diabetes mellitus (IDDM)-cont.

- Prior to the onset of clinically apparent disease, children at risk for IDDM produce antibodies to putative islet  $\beta$  cell autoantigens including glutamic acid decarboxylase (GAD), insulin and the tyrosine phosphatase, IA-2. T cell responses to self-peptides derived from these autoantigens are also made.
- Clinically, the T cell mediated destruction of islet  $\beta$  cells results in an increase in glucose levels, which are normally kept in check by insulin.
- Autoimmune diabetes usually affects young people, who are then dependent on an artificial source of insulin for life. With time severe diffuse vascular abnormalities effecting multiple organs including the heart, kidney, retina and skin occur. In addition, patients are prone to develop the premature onset of atherosclerosis.

### T1DM- a slowly progressive T-cell mediated autoimmune illness



### Inflammatory infiltrate of mononuclear cells in an islet from a 2-year-old patient with type 1 diabetes of short duration



Abner Louis Notkin and Ake Lernmark. Autoimmune type 1 diabetes: resolved and unresolved issues. J Clin Invest, 108, 1247-1252; 2000

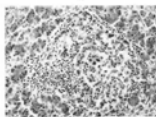
### Autoantigenic Targets of the Autoimmune Response in IDDM

Autoantigen	Antibody	T Cell Responses
Insulin	+	+
GAD65/67	+	+
ICA 105 (IA-2)	+	+
Peipherin	+	+
HSP60	+	+

### Histologic Appearance of Pancreatic Specimens from Patients with IDDM of Recent Onset

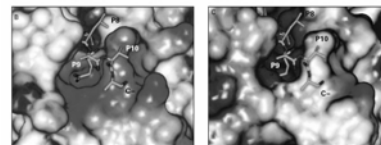
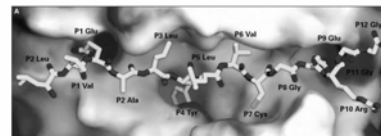


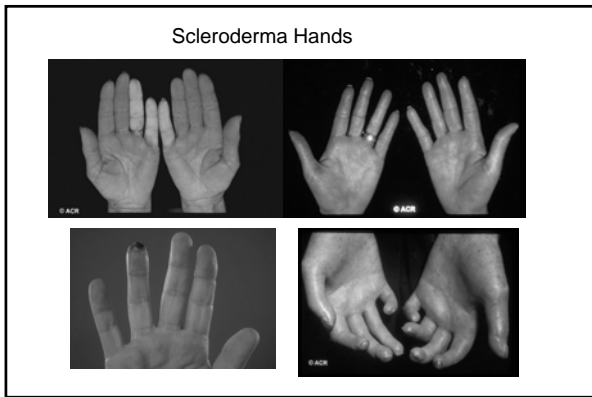
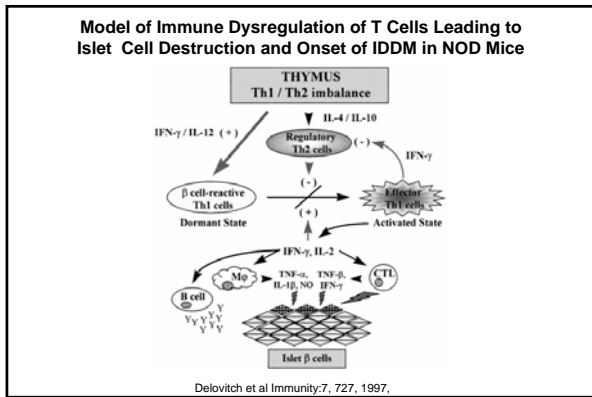
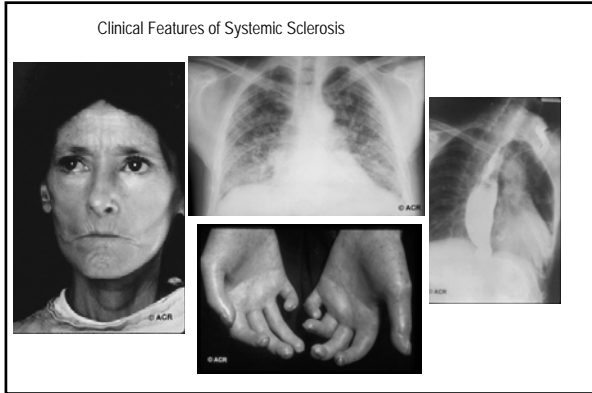
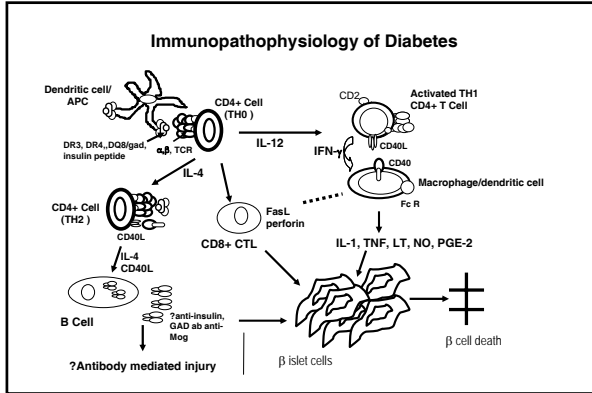
**Later stage of IDDM with clinical signs**  
Panel A shows a section of pancreas stained for glucagon, somatostatin, and pancreatic polypeptide with a method involving alkaline phosphatase (x1150). All endocrine cells are stained, confirming the lack of insulin-containing beta cells.



**Very early stage of IDDM- no clinical IDDM**  
Panel B shows an islet infiltrated with inflammatory cells, a condition often referred to as insulinitis (hematoxylin and eosin, x700).

### Insulin Peptide bound to HLA-DQ8 in IDDM





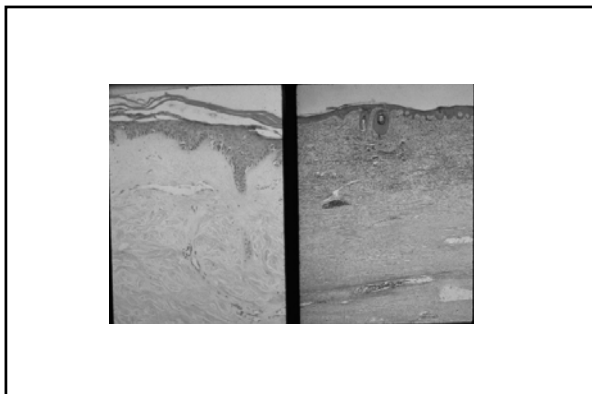
### Scleroderma: Progressive Systemic Sclerosis

**Definition:** Scleroderma is a multi-systemic disease characterized by the excessive accumulation of collagen in skin, GI tract and various other internal organs

**Histopathology:** early there is lymphocytic infiltration and fibroblast proliferation, later there is fibrosis

**Clinical manifestations:** Sclerodactyly, dermal swelling and/or ulceration, esophageal dysfunction, small bowel infection and distention, renal dysfunction, arthritis and in a systemic form "Crest" is associated with calcinosis, raynauds phenomenon and telangiectasia, also associated with pulmonary, and/or renal hypertension.

**Serology:** Scl 70 (DNA Topoisomerase)



### Antibodies Associated With Scleroderma

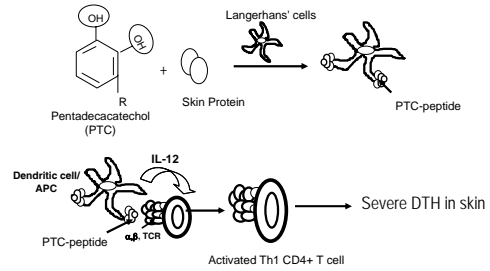
Scl-70 (DNA Topoisomerase I)  
70% Diffuse Scleroderma

Centromere  
70-80% in CREST  
25% Raynaud's Phenomenon

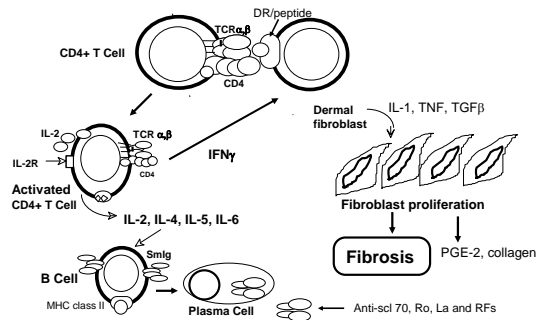
Nucleolar Antigens  
4-8% Scleroderma

PM-Scl  
Polymyositis-Scleroderma Overlap

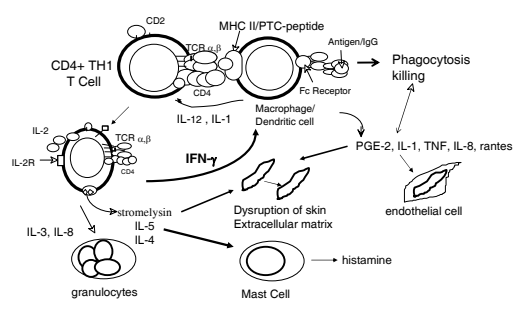
### Sensitization to Poison Ivy and DTH response



### Pathophysiology of Scleroderma



### Physiology of the DTH Response in Contact Hypersensitivity



Blistering skin lesions on the hand of patient with poison ivy contact dermatitis

