Autoimmunity

- Factors predisposing an individual to autoimmune disease
- Mechanisms of initiation of autoimmunity
- Pathogenesis of particular autoimmune disease
- Animal models of autoimmune disease
- Treatment of autoimmune disease

Autoimmunity

- Autoimmune diseases are pathologic conditions that result from the failure of the tolerance mechanisms to specific self antigens
- Positive Selection:
  - T cells interact with self MHC and Self peptides survive
- Negative Selection:
  - T cells interact strongly with self MHC and self peptides are killed
  - B cells that have anti-self antibodies are killed

Targets of Autoimmunity

- Autoimmunity can arise by both T cell and antibody mediated responses
- Some autoimmune diseases are mainly mediated by T cell mediated damage like MS or antibody mediated damage like SLE
- Traditionally grouped according to to the targets of attack
  - Organ-specific autoimmunity
  - Systemic autoimmunity

Genetic Contributions to Autoimmunity

- Some show increased prevalence in families
- In animal models genetic predisposition is an important factor in disease susceptibility
- Multiple genes involved in autoimmune diseases
  - Example :
    - SLE at least 12 genes with low penetrance
    - No one gene marker for susceptibility
- Certain MHC class I and II genes show strong association with certain autoimmune diseases
  - Meaning, those with the disease are more likely than the rest of the population to have a certain HLA haplotype than is found in the general population

Genetic Contributions to Autoimmunity

Table 26.2 Relative risk of some autoimmune diseases

Disease	Associated HLA	Relative risk
Addison disease	DR3/DQ	6.3
AS	B27	87.4
Behçet disease	B5	7.4
IDDM	DR3	5.3
MG	DR3	2.5
RA	DR4	4.2
SLE	DR3	5.8

Environmental Contributions to Autoimmunity

- Environmental agents may provoke or exacerbate a variety of autoimmune disorders
- Infection has been implicated as a direct precipitant of autoimmune diseases
- Example MS:
  - Higher risk in N. latitudes of Europe than S. latitudes
  - Emigrants who moved from N. to S. before age 12 assumed the lower risk level of the S.
  - Emigrants who moved from N. to S. after age 12 retained the N. risk.

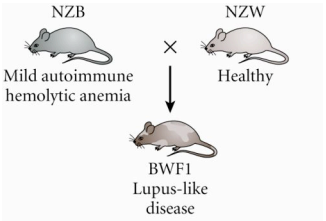
Systemic Autoimmunity

- Systemic Lupus Erythematosis, SLE, Lupus
  - Skin lesions, arthritis, kidney failure, cardiac problems, and neuropsychiatric issues.
  - Polyclonal B cell activation producing IgG Abs
  - Characterized by anti-nuclear antibodies (ANAs)
    - Anti-double stranded DNA abs (anti-dsDNA)
    - Anti-small nuclear ribonucleoproteins (anti-snRNP)
  - 10:1 female to male
  - Risk associations:
    - HLA-DR2 and 3
    - TNF-alpha polymorphism
    - Deficiency in complement C2,C4,C5, and C8

Systemic Autoimmunity Animal Model

- SLE mouse: BWF1
  - Clear preference for females
  - Autoantibodies to dsDNA
  - Fatal lupus nephritis
  - Castration of males makes them susceptible
  - Addition of female hormones to female mice accellerates disease
  - Addition of male hormones to females inhibits disease
  - Antibodies blocking CD4+ T cell activity inhibits disease

SLE mouse



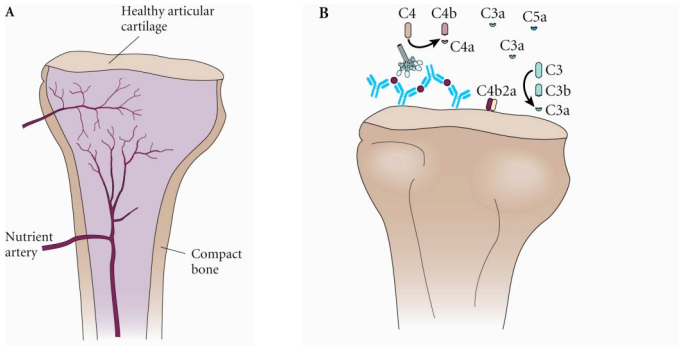
Symptom	% Positive BWF1 mice
Antinuclear antibodies	46
Proteinuria	80
Lupus nephropathy	75
Severe nephropathy	38

The data are from E. D. Dubois et al., *JAMA* **195**:285–289, 1966.

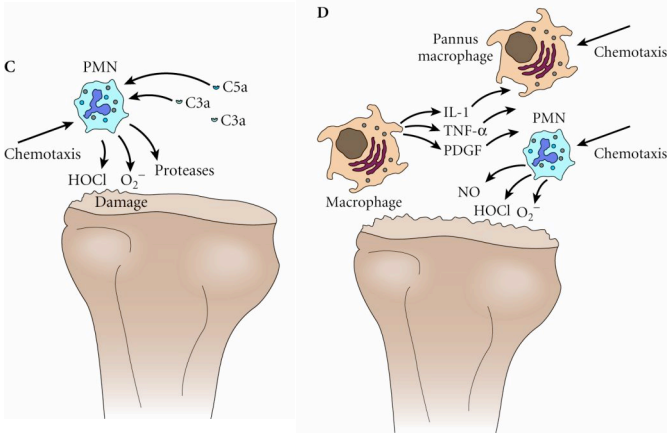
Systemic Autoimmunity

- Rheumatoid Arthritis, RA
  - Peripheral synovial joint arthritis, or degradation of cartilage
  - Antigen-antibody immune complexes lodge in the cartilage and activate complement
  - Complement activation attracts PMNs and macrophages to the joint
    - PMNs release proteases and ROIs and cause joint damage
    - Macrophages release cytokines that attract more immune cells and form a granuloma-like tissue called a pannus
      - Leukocytes in the pannus release more proteases and ROIs and cause even more damage to the joint
  - Etiology remains unknown
    - T cell initiation of disease?
    - Memory T cells in initial stages
    - Infectious or microbial agents?

Rheumatoid Arthritis, RA



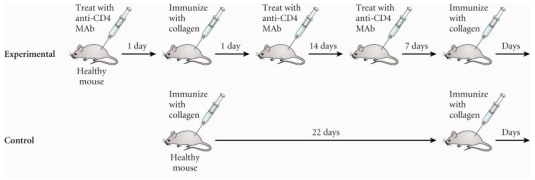
Rheumatoid Arthritis, RA



Animal Models of Rheumatoid Arthritis, RA

- Collagen-induced arthritis (CIA)
- Adjuvant-induce arthritis (AIA)
- Pristane-induced arthritis (PIA) (paraffin oil)
- CIA = intense joint destruction similar to RA
  - T cell mediated and antibody response to collagen; subsequent complement activation

Collagen-induced arthritis (CIA)



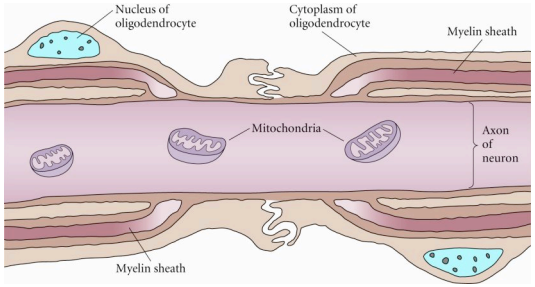
Group	No. with arthritis/ total no. of mice	Mean day of onset
Experimental	2/10	80
Control	9/10	44

Systemic Autoimmunity

- Multiple Sclerosis, MS
  - Tissue-specific etiology but systemic effects
    - Demyelination of neuronal axons in the brain and spinal cord
    - Myelin sheath damage interferes with nerve signal impulse transmission
    - Systemic loss of motor and sensory function
  - Two major forms clinically:
    - Remitting/relapsing and progressive
  - Infiltration of T, B and macrophages into the CNS during disease process
    - Inflammatory cytokines and chemokines
    - Unknown what actually causes the damage to the myelin sheath of the axons
      - Anti MBP T cells and antibodies are found in patients with MS
  - North Americans and European Whites.
    - Prevalence increases with distance from the equator
    - Possible Infectious agents include HHV6, EBV, and *Chlamydia pneumoniae*

Multiple Sclerosis, MS

- Schwann cells (oligodendrocytes) form the myelin sheath of the axons they grow around



EAE as a model for MS

- Experimental Allergic Encephalomyelitis mouse
  - Immunize certain strains of mice with myelin proteins
  - Develop acute disease with spontaneous remission and relapse cycles
  - TH1 cytokines are associated with disease
  - TH2 cytokines are effective at downregulating EAE symptoms

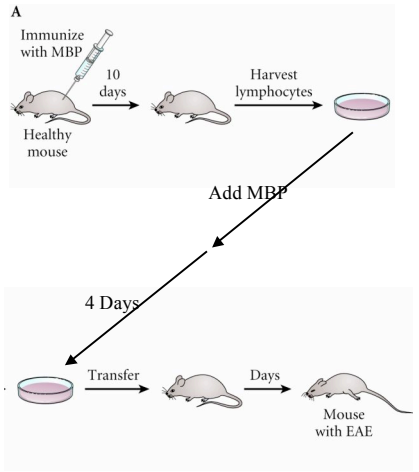
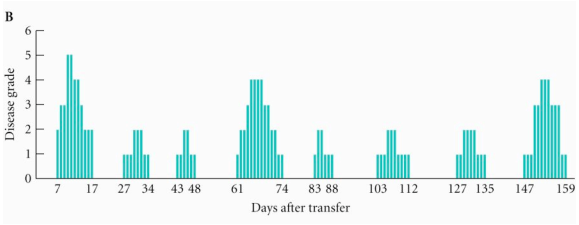


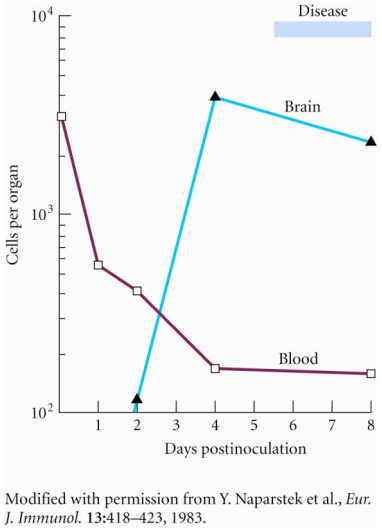
Fig 26.10

EAE as a model for MS

EAE as a model for MS



Remitting and relapsing cycles of disease symptoms



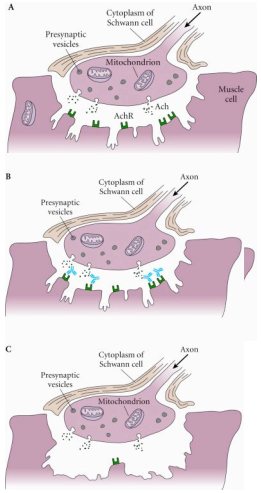
Modified with permission from Y. Naparstek et al., *Eur. J. Immunol.* **13:**418–423, 1983.

EAE as a model for MS

- T cells home to the brain where they mediate destruction of the myelin sheath
- T cells in brain correlates with disease symptoms

Organ-specific Autoimmune Disease

- Myasthenia Gravis, MG
  - Muscle weakness and fatigue are caused by autoantibodies against nicotinic acetylcholine receptors (AChR) at the neuromuscular junction
    - They block binding of ACh to AChR and prevent nerve-signal propagation
    - Complement activation may cause additional damage
  - Young women (20s 30s) and Older men (50s 60s)
  - Molecular mimicry to infectious peptides?



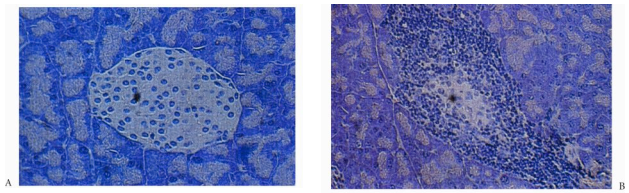
Myasthenia Gravis, MG

Organ-specific Autoimmune Disease

- Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes
  - Cell mediated damage to the pancreatic Beta cells of the islets of langerhans
  - Preclinical insulitis:
    - Infiltration of lymphocytes (CD4+, CD8+ T cells and B cells) and presence of autoantibodies in the islets of langerhans
    - Macrophage are activated by T cells and increase damage
    - T cells specific for insulin, heat shock proteins, islet cell antigens, glutamic acid decarboxylase (GAD)
  - Autoantibodies against cytoplasmic islet cell antigens are found in 80% of patients; can also be found in preclinical patients
  - Effects are systemic
    - Lack of insulin production by beta cells results in hyperglycemia, weight loss, and ketoacidosis
      - Produce chronic metabolic derangements that lead to decreased bloodflow to the extremities
  - Viral infection as a cause?
    - Possible sequence homology between a cytoplasmic islet antigen and coxsackievirus and nucleoprotein in influenza virus
    - Congenital rubella infection has also been correlated

Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes

A. Normal Islets of Langerhans
With Beta cells producing insulin

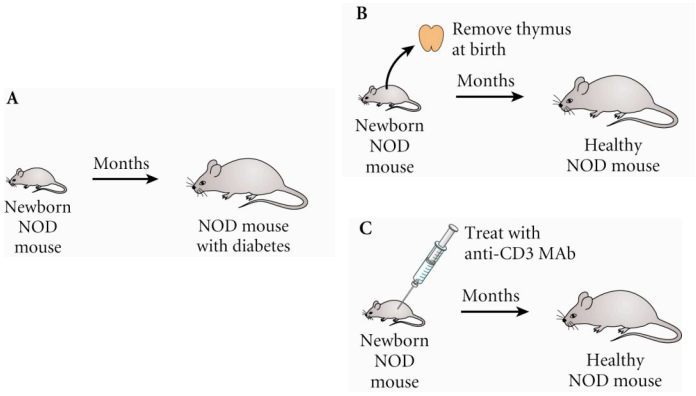


B. Infiltration of Islets of Langerhans with lymphocytes and Destruction of Beta cells

Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes Animal Model

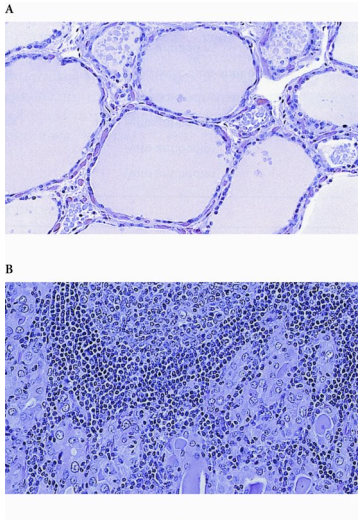
- Nonobese diabetic mouse, NOD mouse
  - Insulitis in almost 100% of the mice
  - 80% females progress to diabetes
  - 30% males progress to diabetes

Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes



Organ-specific Autoimmune Disease

- Chronic autoimmune thyroiditis: HT and GD
  - Hashimotos thyroiditis, HT
    - Inflammatory thyroid characterized by a goiter with or without hypothyroidism
    - Cellular infiltration and autoantibodies in thyroid
    - Loss of thyroid function probably due to autoantibodies against TSHR
    - 2:1 female to male
  - Graves Disease, GD
    - Hyperthyroidism and goiters
    - Stimulatory autoantibodies against TSHR causing thyroid growth and increase in thyroid hormones
    - 10:1 female to male
  - Viral infections?

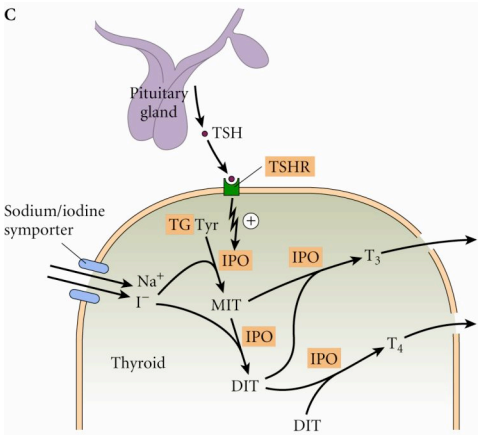


Hashimotos thyroiditis, HT

- A.
- Normal thyroid tissue

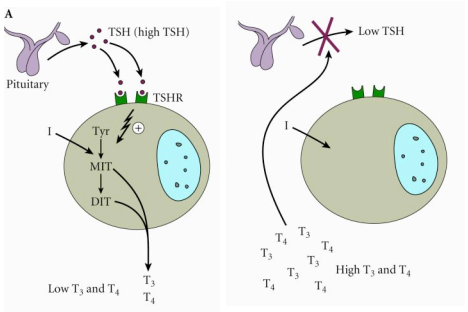
- B.
- Intense lymphocyte infiltration

Hashimotos thyroiditis, HT



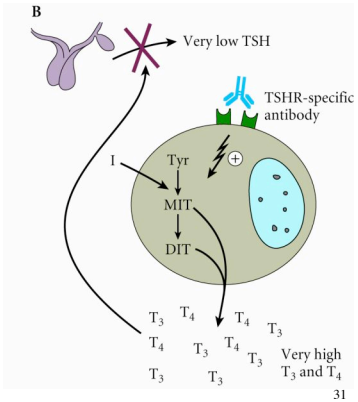
Graves Disease, GD

- Normal regulation of thyroid hormone production
- Feedback inhibition of products



Graves Disease, GD

- Anti-TSHR antibody stimulates TSHR signal transduction and causes thyroid to produce even more products
- Subverts feedback inhibition



Animal models of autoimmune thyroiditis

- Obese chicken
  - Resembles HT
  - Hypothyroidism, cellular infiltration into thyroid
- NOD mice and BB rats also have a low incidence of thyroiditis along with diabetes