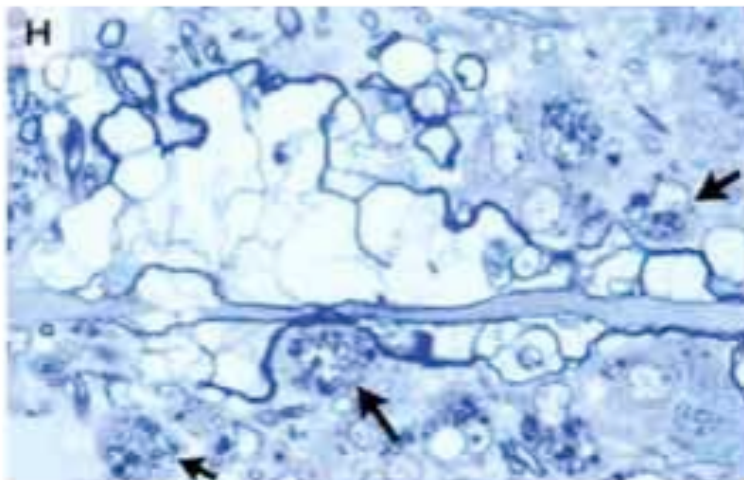
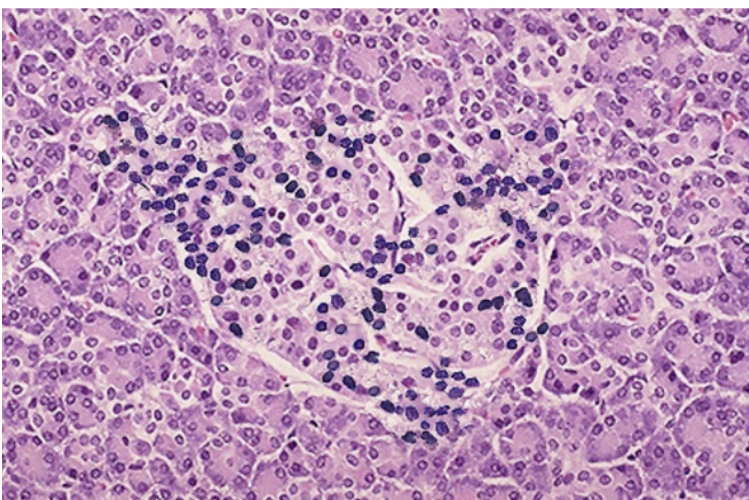


# Lecture 22. Multiple Sclerosis and Type I Diabetes Mellitus

## Learning Objectives and Summary



Toluidine blue stain of a longitudinal section of the myelin sheath surrounding an axon at the margin of an acute lesion of MS. Vacuolation and vesiculation are present and accompanied by macrophages next to the degenerating myelin (*arrows*). Macrophages are filled with droplets of myelin, suggesting that macrophages phagocytose myelin and associated cellular debris. From: Frohman et al., *New Engl. J. Med* 354:942, 2006.



An islet of Langerhans demonstrates insulinitis with lymphocytic infiltrates in a patient developing type I diabetes mellitus. This lesion precedes clinical onset of diabetes mellitus. (<http://medlib.med.utah.edu/WebPath/TUTORIAL/DIABETES/DIAB002.html>)

## 22. Multiple sclerosis and Type I Diabetes Mellitus

### Learning objectives:

1. Understand the various clinical forms and features of Multiple Sclerosis (MS)
2. Understand the immune pathogenesis of MS
3. Appreciate the immunological basis of some of the therapeutic approaches to MS
4. Understand factors that cause or trigger Type 1 diabetes mellitus (DM) and review the immune mechanisms involved
5. Learn how to screen populations at risk for developing Type I DM
6. Discuss developing therapies aimed at prevention or immune modulation of DM

### SUMMARY

1. MS is a chronic typically relapsing/remitting disease of the CNS resulting from demyelination, producing “plaques” on MRI and pathological sections.
2. The hallmark of MS plaques are perivascular infiltration by lymphocytes, parenchymal edema, loss of myelin and oligodendrocytes, axonal damage, plasma cells, and activated macrophages.
3. Accumulating evidence indicates that pro-inflammatory cytokines from antigen presenting cells and T cells are required for development of the MS plaque. IL-12 and/or IL-23 are released from APCs and stimulate release of IFN- $\gamma$  or IL-17, respectively, from activated T cells. In animal models of MS (e.g., experimental autoimmune encephalomyelitis, or EAE) one or more of the cytokines are required for CNS pathology.
4. FDA-approved treatment options include Interferon beta (blocks Ag presentation, cellular adhesion, synthesis of MMPs), Glatiramer acetate (increases Tregs, suppresses Th1 cytokines and shifts balance to Th2 cytokines) and Mitoxantrone (reduces Th1 cytokines and eliminates lymphocytes). Possible adjunctive therapy includes corticosteroids, azathioprine, and methotrexate.
5. Type I diabetes is an autoimmune disorder in which beta cells of the pancreatic islet are specifically targeted and destroyed. It accounts for 5-10% of all diabetes.
6. While the cause of type I diabetes is not entirely understood there are well described genetic susceptibility loci including MHC and CTLA4. Concordance in monozygotic twins is 40% indicating that environmental factors are also involved.
7. The immune response to pancreatic antigens involves both CD4 and CD8 cells. CD8 cells destroy beta cells but require help from CD4 cells. B cells may be important APC's in this disease. Infiltrating cells have a Th1 profile.
8. Regulatory T cells are important in controlling progression and are relatively depleted in established disease.
9. Relatives can be screened by immunologic assays for risk of diabetes development with high sensitivity and specificity.

10. Immune prevention strategies are currently being evaluated and new methods are being developed for islet cell transplantation.