Case 23

C.G. is the only child born to his parents. His growth and development were normal and he excelled at school. When he was 6 years old he began to lose weight and developed enormous thirst such that he was consuming over three liters of liquid a day. The thirst and excess fluid consumption was accompanied by frequent urination. He was taken to the family doctor who found the patient was hyperglycemic and diagnosed with Type 1diabetes mellitus. It turned out that a paternal uncle had also developed juvenile-onset diabetes.

C.G. was started on diet and daily insulin injections. His blood glucose was easy to control in the first 6 months after diagnosis, but then became more difficult. He experienced glucose levels over 200 mg/dl after meals and about three episodes of hypoglycemia (glucose level < 70 mg/dl) each week. His hemoglobin A1c levels (a measure of chronic glucose control) were generally 8.0 – 9.0% (nl to 6.0%). When he was 35 years old, a routine annual physical examination revealed an elevated blood pressure and proteinuria (presence of increased protein in the urine). A serum creatinine was 7.5 mg/dl (normal < 1.2 mg/dl). On the basis of this result, Christopher's physician suspected that he had developed renal complications of diabetes. An ultrasonogram of the kidneys revealed small kidneys bilaterally (evidence of chronic, irreversible renal failure). He ultimately underwent hemodialysis (passing blood over a semi-permeable membrane to remove waste products such as urea) twice weekly. He had few dialysis-related complications but had several episodes of ulcerations and cellulitis (inflammation of the skin, usually infectious in etiology) of both feet. He was put on a waiting list for a kidney transplant; as part of his pre-transplant evaluation, he was found to be blood group B, Rh-positive; HLA A2,24; B50,51: DR3,4, DQA1-0501, DQB1-0201, and DQA1-0301 and DQB1-0302.

Questions for Case 23

(1) There was little family history of juvenile diabetes for this patient, yet the disease has been linked to genes of the MHC. Can you suggest a genetic or environmental interaction that might explain this discordance?

(2) C.G. is HLA-DR3,4 and has DQ alleles highly associated with Type 1 diabetes (about 50 times more than individuals without these alleles). How might specific MHC class II alleles confer increased susceptibility to IDDM?

(3) Insulin, proinsulin, GAD65, all thought to be important autoantigens, are expressed in the thymus. Although many patients with Type I DM have detectable circulating antibodies against these antigens, not all do. What does this tell us about the pathogenesis of Type I DM and autoimmunity, in general?

(4) In addition to HLA genes, susceptibility to Type I DM has been mapped to several other loci. For example, DM-susceptible loci map to genes encoding CTLA-4 and PTPN22, a protein tyrosine phosphatase expressed preferentially in T cells). Speculate as to whether polymorphisms in these genes associated with Type I DM encode loss-of-function or gain-of-function variants and describe how they might be involved in development of the disease.