Introduction

The aim of the Diabetes Prevention Trial-1 (DPT-1) was to prevent type 1 diabetes (T1D) by administering insulin in a tolerizing context, either orally or parenterally, to antibody-positive relatives. The absence of any observable effect from these interventions [1] was particularly disappointing because both had been proven effective in the two animal models of spontaneous autoimmune diabetes, the nonobese diabetic (NOD) mouse [2] and the BioBreeding diabetes-prone (BBDP) rat [3]. The failure brings renewed interest to the question of how relevant these animal models are to the human disease. There is no simple answer to this question. It is clear that we can learn, and have learned, much that is relevant to human T1D from these models. It is also clear, to most of us, that there are limits to how much we can extrapolate from them. Where these limits are and what their exact nature is, are much more difficult questions whose detailed dissection is outside the scope of this short article; the reader is referred to a recent review summarizing the immunologic aspects [4]. In this article I only discuss genetic heterogeneity in the human disease, an aspect that is rarely discussed in this context but which I believe to be of crucial importance in understanding what the animal models can tell us and what they may not tell us.

Of Mice and Rats

To stimulate some thinking, I will reverse the question: Would human T1D be a good model for studying diabetes in the NOD mouse and the BBDP rat? Or, to avoid the complexities of research on humans, a simpler question: is NOD a good model for studying BBDP? And vice versa? This is a simpler question and the ethical constraints of human research are not the most important reason why. More importantly, the animal models represent inbred strains where all individuals are identical genetically and universally homozygous, thus the equivalent of studying one human patient in multiple copies, a patient who is homozygous at every genetic locus.

It is generally accepted that T1D results from the autoimmune destruction of the insulin-producing pancreatic β cells. The presence of autoantibodies [5], dependence on HLA genotype [6], coexistence with other autoimmune diseases, and the scant but compelling autopsy data [7,8] all converge to support the notion that human T1D is essentially due to the same process that destroy the β cells in the animal models: a breakdown in self-tolerance involving cellular immunity, very specific to the β cell and mediated by massive infiltration of the islets of Langerhans by lymphocytes and macrophages (insulitis). Just as in the NOD mouse and the BBDP rat, human T1D begins at a young age, is associated with anti-islet autoantibodies, and ends with the total or quasi-total destruction of the β-cell mass. Does it follow that the disease has the same etiology? The answer is not automatically yes.

Type 1 diabetes concordance in monozygotic twins approaches 50%, indicating that although it does not explain all, genetic susceptibility is important. In the two animal models, environment does alter frequency and severity of diabetes, but no amount of environmental manipulation can induce the disease in the absence of a susceptible genetic background. Because not a single environmental factor has
been definitely proven as being involved in human T1D. I
confine this discussion to genetics. However, the underly-
ing principle (human phenotypic heterogeneity) may be
extended to the effects of environmental factors when we
know more about them.

Genetically, the NOD mouse, BBDP rat, and human T1D
all share a remarkable dependence on genotype at the major
histocompatibility complex (MHC) locus as do most autoim-
mune diseases, because of the importance of the encoded
proteins in antigen presentation and their encoding by what
is by far the most polymorphic coding sequences in the
human genome. The NOD mouse carries a unique haplotype
that includes the H2q7 allele at the I-A locus (histidine as resi-
due 56 and serine as residue 57, homologous to “diabeto-
genic” HLA-DQ b nonaspartic acid at position 57, which
explains most of the HLA effect in human T1D) and a null
allele at I-Ea (homologous to human DR1). The correspond-
ing BBDP class II allele is RT6+). Congenic studies in both the
NOD mouse and BBDP rat clearly show that a diabetes-prone
MHC is necessary but not sufficient for diabetes susceptibil-
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15% of the general population carrying the protective
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tions of the immune phenotype. Within the constraints of
human research (essentially limited to examining peripheral
blood cells), have NOD-like mouse immune defects been
seen in human patients with T1D? An attempt at even sum-
marizing the vast literature on immune abnormalities in
humans with T1D is outside the scope of this short report.
Much of it dates to one or two decades ago and little of it has
subsequently been confirmed and followed up. Even the
most convincing examples, where immune dysfunction is
shown, demonstrate a large overlap between patients and
normal control subjects [22–24]. This is not surprising. NOD
mice show consistent differences from other strains because
they all share the same genotype (as well as the same environ-
mental determinants). Being much more genetically diverse,
human patients need not have such uniformity.

Ultimately, autoimmune disease results from a disruption
in the delicate equilibrium the immune system has to main-
tain between defending against infection and respecting self.
Each side in this balance of conflicting priorities is weighed
upon by several functional pathways that promote host-
defense responses and others that promote self-tolerance. The
end point (insulitis and β-cell destruction) may be arrived at
through any combination of disruptions in these pathways.