Paratuberculosis and Type I diabetes
Is this the trigger?

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Summary
Type 1 diabetes mellitus (T1DM) is an autoimmune disease. The etiology of T1DM is incompletely understood but environmental agent(s) are thought to trigger T1DM in the genetically at risk. Exposure to cow’s milk early in life is a recognized risk factor in the development of T1DM. Mycobacterium avium ss. paratuberculosis (MAP) is the cause of bovine Johne’s disease and also is thought to act as an immune antigen in Crohn’s disease and other granulomatous diseases. MAP is shed in cow’s milk and has been shown to survive pasteurization. Genetic susceptibilities, epitope homologies and epidemiologic studies are presented that support MAP as a causative agent of T1DM in the genetically at risk.

Introduction
The cause of Type 1 diabetes (T1DM) is unsolved. It thought to be caused by a combination of genetic and environmental factors. It is an autoimmune disease in which T lymphocytes infiltrate the islets of the pancreas and destroy the insulin-producing beta cell population [1]. This paper postulates a causative role for Mycobacterium avium ss. paratuberculosis (MAP), acting as an environmental agent that triggers T1DM in the genetically susceptible individual. Three links are offered to support this postulate:

(1) shared genetic susceptibility to both mycobacterial infection and autoimmune diseases, including T1DM;
(2) epitope homologies between mycobacterial elements and pancreatic glutamic acid decarboxylase (GAD);
(3) an alternative interpretation of the epidemiologic findings that launched a large study the Trial to Reduce Type 1 Diabetes in the Genetically at Risk (TRIGR).

MAP
Mycobacterium avium ss. paratuberculosis (MAP) is an obligate intracellular organism that causes a transmural enteric granulomatous disease in
ruminant animals, Johne’s disease [2,3]. MAP is also a suspected to have a causative role in Crohn’s disease, an enteric granulomatous disease of humans [4–8]. Traditional methods of detecting bacteria, culture and stain, have largely been ineffective in detecting MAP in humans [9–11]. The advent of bacterial DNA detection with polymerase chain reaction (PCR) has greatly aided the detection of mycobacteria [12–14] and the DNA of MAP has been found in greater than 90% of biopsy specimens from individuals with Crohn’s disease [15]. Employing newer culture methods Naser reported the detection of MAP bacteremia in a substantial number of patients with Crohn’s disease. MAP has been found to survive pasteurization in retail milk [16] and cheese [17]. Additionally, MAP has been found in granulomas of sarcoidosis [18].

**Shared genetic susceptibilities**

Analysis of multiple populations shows that T1DM is increasing at an incidence of 3% per year since 1960 [19]. Historically, genetic association with T1DM has been established for three chromosomal regions: HLA DQ/DR (IDDM1), INS VNTR (IDDM2) [20] and CTLA-4 (cytotoxic lymphocyte antigen-4) [21].

More recently, susceptibility genes for T1DM have been identified to include the NRAMP-natural resistance-associated macrophage protein gene (also known as SLC11A1) [22,23] as well as the VDR gene (vitamin D receptor) [24,25].

**NRAMP**

NRAMP (natural resistance-associated macrophage protein) is a gene that encodes a divalent cation transporter in phagosomes of macrophages [26]. NRAMP modulates the cellular environment in response to activation by intracellular pathogens by acidifying the phagosome [27]. As such, it plays a role in host innate immunity [28]. Mutation of NRAMP impairs phagosome acidification yielding a permissive environment for the persistence of intracellular bacteria [29].

**VDR**

In addition to a role in the regulation of bone and mineral metabolism, Vitamin D is a potent modulator of the immune system [30]. Vitamin D activity occurs via the vitamin D receptor (VDR). VDR is part of the steroid receptor super-family and is widely express in many cell types including lymphocytes, macrophages and the insulin producing pancreatic beta-cells [25]. Vitamin D and its receptor, VDR, have been implicated in the genetic pathogenesis of T1DM: VDR gene polymorphisms have been described in T1DM in Taiwanese [31], Indian Asians [32], Germans [33], Spaniards [34], Japanese [35] and Croatians [36]. Additionally, calcitriol — the hormonal form of vitamin D — prevents or markedly suppress experimental T1DM [37]. In addition to T1DM, NRAMP and VDR polymorphisms also confer susceptibility to other autoimmune diseases [25,37], and to infection — most notably, mycobacterial infection [25,38,39].

**Molecular mimicry**

It has been proposed that epitope homology between infectious agents and host proteins give rise to molecular mimicry that can induce autoimmune disease [40]. Specific to T1DM is that postulate that cross-reactive microbial antigens in a genetically susceptible host is the critical event leading to the autoimmune destruction of insulin-producing beta-cells of the pancreas [41]. Heat shock proteins are a highly conserved group of chaperone proteins expressed in cells exposed to elevated temperatures or other forms of environmental stress. Hsp65 is a heat shock protein that is unique to mycobacteria [42]. There is an important role for heat shock proteins in autoimmunity and infection; glutamic acid decarboxylase (GAD), the prime antigen of Type 1 diabetes, has similar amino acid sequences to Hsp65 and Hsp65 "should not be completely discarded as having a possible role in the development of Type 1 diabetes" [43]. In a study of children newly diagnosed with Type 1 diabetes 47/47 were found to respond to mycobacterial Hsp65 [44].

**Epidemiologic evidence**

**T1DM and milk**

Several studies indicate an association between early exposure to dietary cow’s milk proteins and an increased risk of T1DM [45–47]. These studies have centered around the observation that children at risk for T1DM who were breast fed exclusively for more than six months were less likely to have T1DM later in life than similar risk children who were weaned onto cow’s milk-based formula at an ear-
lier age. This observation spawned a large study, the TRIGR study: Trial to Reduce IDDM in the Genetically at Risk [48]. Driving the study is the postulate that there is something about cow’s milk protein that is an immunologic trigger for TIDM and that breaking the protein with hydrolysis will eliminate the trigger.

The TRIGR study is an ongoing, 17-country study enlisting 6200 infants who are genetically at risk to develop TIDM. Children weaned early from breastfeeding are randomized into two groups; one receiving traditional cow’s milk-based formula and the other receiving formula in which the protein has been hydrolyzed. This is an ongoing study. MAP has been found in infant formula powder [49].

## Discussion

This paper postulates that *Mycobacterium avium* ss. *paratuberculosis* (MAP) acts as an immune antigen in the pathogenesis of T1DM. As the link between MAP and Crohn’s disease becomes more compelling, MAP is increasingly recognized for its ability to act as an occult antigen. Genetic evidence suggests that there are states of macrophage dysfunction that promote both T1DM and mycobacterial infection. These states can be viewed as templates of macrophage incompetence that individually or in combination allow obligate intracellular pathogens such as MAP to persist and serve as immune antigens. Viable MAP has been found in commercial milk and infant formula. The epidemiologic association of TIDM with early exposure to milk and infant formula. The epide-

## References


[13] O’Mahony J, Hill C. A real time PCR assay for the detection and quantitation of *Mycobacterium avium* subsp. *paratu-


