11

Environmental Triggers of Type 1 Diabetes Mellitus – Mycobacterium Avium Subspecies Paratuberculosis

Coad Thomas Dow[1] and Leonardo A. Sechi[2]
[1]*University of Wisconsin, Eye Research Institute*
[2]*University of Sassari*
[1]*USA*
[2]*Italy*

1. Introduction

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. In the United States the prevalence of T1DM is increasing and is approximately 1 in 300 by 18 years of age. Research into risk factors for T1DM is an active area with attempts to identify genetic and environmental triggers that could potentially be targeted for intervention (Maahs et al., 2010).

The most important autoimmune diabetes triggering factors are thought to be infectious, dietary, perinatal, and/or psychosocial. Historically, enteroviruses (especially Coxsackie B virus) have been the most commonly regarded infectious triggering agents (Peng & Hagopian, 2006).

Evidence supports the critical role of exogenous factors in the development of T1DM: 1. less than 10% of individuals with HLA-conferred diabetes susceptibility progress to clinical disease, 2. pair-wise concordance of T1DM of less than 40% among monozygotic twins, 3. more than 10-fold difference in the disease incidence among Caucasians living in Europe, (annual rate Macedonia 3.2/100,000 vs. Finland 54/100,000) 4. several-fold increase in the incidence over the last 50 years, and 5. migration studies that indicate disease incidence increases in population groups who have moved from a low-incidence to a high-incidence region. (Knip et al., 2005).

The postulate that MAP plays a causal role in T1DM was presented at the 2005 Colloquium on Paratuberculosis (Dow, 2005) and published in 2006 (Dow, 2006). To understand the rationale of the hypothesis it is necessary to review MAP, the role MAP plays in animal disease and the proposed role MAP has in human disease.

2. Mycobacterium avium ss. paratuberculosis (MAP)

MAP is a gram-positive, acid-fast staining small rod-shaped bacterium. As with members of the Mycobacteriaceae genus, it has a unique cell wall structure rich in complex lipids (fig. 1). The thick and chemically distinctive cell wall of mycobacteria is responsible in large measure for the robust nature of these bacteria, both within the host cell and in the

environment. The pathogenic potential of mycobacteria is correlated with their growth rate. Paradoxically, slow-growing mycobacteria are more virulent than fast-growing mycobacteria. With the exception of *Mycobacterium leprae* (the cause of leprosy in humans), which cannot be cultured in vitro, MAP has the slowest growth rate of pathogenic mycobacteria. After isolation from infected animals and grown under optimal conditions colonies of MAP are typically not visible for 3 months or more (Collins, 2003).

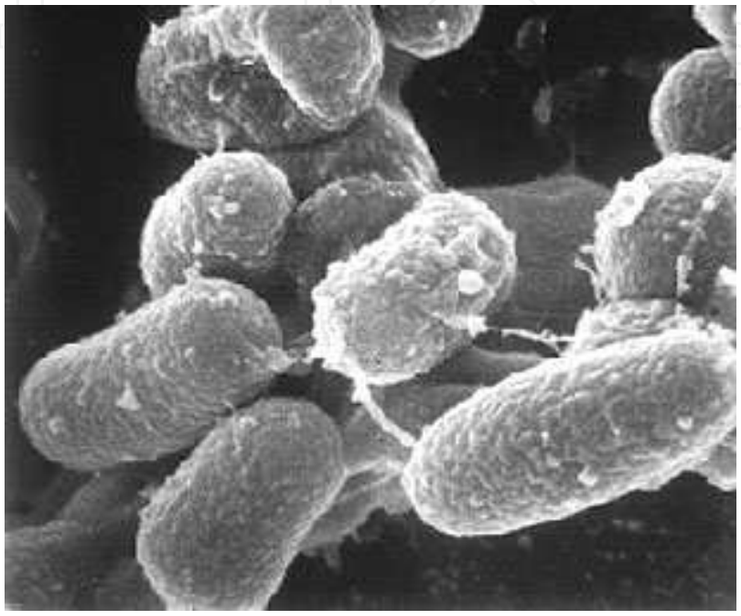

Fig. 1. Electron Microscopy of Mycobacterium avium ss. paratuberculosis (MAP).
Image courtesy of Dr. Mike Collins, University of Wisconsin – Madison.

Mycobacterium avium subspecies *paratuberculosis* (MAP) causes a chronic granulomatous inflammation of the intestines in ruminant animals called Johne's disease. Mostly studied in dairy cattle, goats and sheep, MAP also causes a chronic inflammation of the intestines in beef cattle and in a wide variety of other domestic and wild ruminants. MAP-induced enteric inflammation has been found in monogastric animals including dogs and pigs as well as four different types of subhuman primates – macaques, baboons, gibbons and cotton-top tamarins'' (Hermon-Taylor et al., 2000). A majority of the dairy herds in the United States and Europe have infected animals within the herd (Stabel, 1998).

2.1 MAP and human exposure

The article*, Evolutionary bottlenecks in the agents for tuberculosis, leprosy and paratuberculosis* (Frothingham, 1999), indicates that these parasitic mycobacteria are different from the ''environmental'' mycobacteria and may reflect opportunities afforded the parasitic mycobacteria by human cohabitation with domesticated animals combined with consolidation of populations. More crowded conditions may have changed tuberculosis, leprosy, and paratuberculosis from sporadic to epidemic diseases.

Mycobacterium avium ss. *paratuberculosis* (MAP)is present in pasteurized milk (Millar et al., 1996; Ellingson et al., 2005), infant formula made from pasteurized milk (Hruska et al, 2005), surface water (Pickup et al., 2005; Whan et al., 2005; Pickup et al, 2006), soil (Pickup et al.,

2005), cow manure ''lagoons'' that can leach into surface water, cow manure in both solid and liquid forms that is applied as fertilizer to agricultural land (Grewal et al., 2006), and municipal tap water (Collins, 2003), providing multiple routes of transmission to humans. In a recent study in Ohio the DNA of MAP was detected in over 80% of domestic water samples (Beumer et al., 2010).

Normal water treatment processes such as filtration and chlorination amplify rather than eliminate mycobacteria organisms by killing off their competitors (Falkinham, 2003). In addition, mycobacteria organisms grow on tap water pipes (Falkinham & Norton, 2001), in biofilms (Vaerewijck et al., 2005) and on plastic water bottles (Tatchou-Nyamsi-Konig et al., 2009). It is estimated that mycobacteria may be present in drinking water in "massive numbers," on the level of up to 700,000 or 7 x 105 organisms per liter of water (Falkinham et al., 2001).

3. MAP and human disease – inflammatory bowel disease and sarcoidosis

Beyond Johne's disease of animals, MAP is the putative cause of the striking similar Crohn's disease of humans. Although there has been a century-long debate, the role of MAP in Crohn's has evolved from controversial to compelling (Chamberlin et al., 2007; Feller et al., 2007; Mendoza et al., 2010). The major source of the debate is that conventional methods of detecting bacteria – namely, culture and stain - are largely ineffective in detecting MAP. However, with newer laboratory techniques, primarily PCR, evidence of MAP is readily found in Crohn's tissues (Chiodini, 1989; McFadden et al, 1987); it can be visualized within the granulomas by in situ hybridization (Sechi, 2001): and, with extreme care and patience, MAP can be grown from the gut and blood of Crohn's patients (Naser et al., 2004, 2009; Sechi et al., 2005).

MAP has also been reported as a candidate pathogen in the causation irritable bowel syndrome (Scanu et al., 2007) and some suspect that MAP causes the spectrum of inflammatory bowel disease including Crohn's, ulcerative colitis and irritable bowel syndrome (Pierce, 2010). Irritable bowel syndrome is a widespread abdominal condition that affects about 10 to 15% of people in the industrialized economies of Europe, North America, Australasia, and Japan, with a rising prevalence among the populations in the developing economies of Asia. Some consider irritable bowel syndrome a *form fruste* of Crohn's disease (Olbe, 2008).

In addition to inflammatory bowel disease MAP has been historically linked is sarcoidosis; a multi-system inflammatory disease in which DNA evidence of MAP has been found (sporadically) in sarcoid granulomas (el-Zaatari, 1996).

4. Genetics and T1DM

Early studies indicated that the HLA region on chromosome 6p21 (commonly termed IDDM1, for insulin-dependent diabetes mellitus locus) is a critical susceptibility locus for T1DM (Nerup et al., 1974; Singal & Blajchman, 1973). A comprehensive review of the genetics of T1DM is beyond the scope of this chapter; instead, we will focus on genes that appear to be permissive to MAP (CARD15 and SLC11A1) and then to MAP and T1DM specifically (SLC11A1). Though we will focus on these genes, it is short sighted to expect that only one or two genes affect the susceptibility of humans to mycobacterial infections and autoimmune disease. Gene-gene interaction (epistasis) is known with regard to tuberculosis susceptibility (de Wit et al., 2010). For instance, there seems to be a role for

vitamin D as well as the VDR gene (vitamin D receptor) (Hayes et al., 2003; Motohashi et al., 2003). In addition to regulation of bone and mineral metabolism, Vitamin D is a potent modulator of the immune system (Zella & DeLuca, 2003). Vitamin D activity occurs via the VDR. VDR is part of the steroid receptor super-family and is widely expressed in many cell types including lymphocytes, macrophages and the insulin producing pancreatic beta-cells (Hayes et al, 2003). Vitamin D and VDR, have been implicated in the susceptibility of TIDM: VDR gene polymorphisms have been described in TIDM in Taiwanese (Chang et al., 2000), Indian Asians (McDermot et al., 1997), Germans (Pani et al., 2000), Spaniards (Marti et al., 2004), Japanese (Ban et al., 2001) and Croatians (Skrabic et al., 2003). Additionally, calcitriol – the hormonal form of vitamin D – prevents or markedly suppress experimental TIDM (Deluca & Cantorna, 2001) and is active against tuberculosis (Jo, 2010).

4.1 Genetics – CARD15

The CARD15 gene is part of the ancestral innate immune system that senses and eliminates bacteria (Girardin et al., 2003; Hugot et al., 2002; Inohara et al., 2003); it is part of the newly recognized, larger CATERPILLER gene family that acts as sensors to detect pathogens and regulates inflammatory and apoptotic responses (Ting & Davis, 1985). Defects in the CARD15 gene are associated with Crohn's disease susceptibility (Hampe et al., 2002). In 2005, Sechi reported that more than 70 percent of people in Sardinia with Crohn's disease carry at least one of the susceptibility-associated NOD 2/CARD 15 alleles and were infected with MAP.

Insights into genetic susceptibility and MAP infection can be found in a rare inflammatory disease, Blau syndrome. Blau syndrome is an inherited granulomatous inflammatory disorder with clinical findings of uveitis, arthritis, and dermatitis (Blau, 1985). Although rare, Blau syndrome has been of interest in current medical literature because of the discovery that places its genetic defect on the same Crohn's susceptibility CARD15 gene (Hampe et al., 2002; Miceli-Richard et al., 2001). Linkage studies have placed the gene on chromosome 16; originally referred to as the NOD2 gene, it is now known as the CARD15 gene (Hugot et al., 2002). The Blau syndrome susceptibility component of the CARD15 gene is at the nucleotide binding site domain (Hampe et al., 2002; Wang et al., 2002) while the Crohn's susceptibility is at the N-terminal leucine-rich repeat domain (Hugot et al., 2002; Lesage et al., 2002). The CARD15 gene is part of the ancestral innate immune system that senses and eliminates bacteria (Girardin et al., 2003; Inohara et al., 2003).

The clinical findings of Blau syndrome are one and the same as juvenile sarcoidosis; and, indeed, de novo CARD15 defects are consistently found in cases of sporadic juvenile sarcoidosis – Blau syndrome (Kanazawa et al., 2005; Rose et al., 2005). For these reasons - the clinical appearance of sarcoidosis and a shared genetic susceptibility with Crohn's - it was proposed that MAP could have a role in Blau syndrome. The following results were presented at the 2005 Colloquium on Paratuberculosis (Dow) and published in 2010 (Dow & Ellingson, 2010):

> *Methods. Archival tissues of individuals with Blau syndrome were tested for the presence of MAP. Results. DNA evidence of MAP was detected in all of the tissues. Conclusions. This article finds that MAP is present in Blau syndrome tissue and postulates that it has a causal role. The presence of MAP in Blau syndrome – an autosomal dominant, systemic inflammatory disease – connects genetic and environmental aspects of "autoimmune" disease.*

The complexity of genetic susceptibility and microbial infection can be reflected in these two diseases (Crohn's and Blau), both having polymorphisms of the CARD15 gene. The proposed etiopathology is that with adequate MAP exposure, an individual with SNPs within one CARD15 location (nucleotide binding domain) will exhibit Blau syndrome and if

the SNPs are within another location of the same gene (leucine-rich-repeat domain) they exhibit Crohn's disease. CARD15 defects of the leucine--rich-repeat domain, result in an aggressive phenotype of Crohn's disease (Lacher et al., 2010). Adding to the complexity is that there are several susceptibility genes associated with Crohn's (Franke et al., 2010).

4.2 Genetics - SLC11A1

One additional gene associated with Crohn's susceptibility is the SLC11A1 gene (Sechi et al., 2006). Natural resistance-associated macrophage protein 1 (NRAMP1) is now strictly referred to as SLC11A1 (solute carrier 11a1). The gene that encodes for this protein is recognized as having a role in the susceptibility of humans and animals to a number of infections, including mycobacterial infections, and is associated with a number of autoimmune diseases as well. In human beings, the SLC11A1 gene is located on chromosome 2q35. It encodes an integral membrane protein of 550 amino acids that is expressed exclusively in the lysosomal compartment of monocytes and macrophages (Canonne-Hergaux et al., 1999).

The product of the SLC11A1 gene modulates the cellular environment in response to activation by intracellular pathogens by acidifying the phagosome thus killing the pathogen (Lapham et al., 2004). As such, it plays a role in host innate immunity (Wyllie et al., 2002). Mutation of SLC11A1 impairs phagosome acidification yielding a permissive environment for the persistence of intracellular bacteria (Hackam et al., 1998).

5. SLC11A1 in infectious and autoimmune disease

Sarcoidosis, the previously mentioned systemic disease associated with MAP, is also associated with polymorphisms of the SLC11A1 gene (Dubaniewicz et al., 2005). Susceptibility to mycobacterial diseases tuberculosis, leprosy and Buruli's ulcer are associated with polymorphism of the SLC11A1 gene (Stienstra et al., 2006). Similar polymorphisms are associated with Johne's disease (paratuberculosis) in cattle (Ruiz-Larrañaga et al., 2010), goats (Korou et al., 2010), and sheep (Purdie et al., 2011). When researchers at the Belgium Pasteur Institute developed a murine model for MAP infection, they created an SLC11A1 defect mouse (Roupie et al., 2008).

Given the pivotal roles that SLC11A1 plays in innate immunity, it is not surprising that the relationship between polymorphisms in SLC11A1 and a number of mycobacterial as well as autoimmune diseases has been explored (Blackwell et al, 2003). Associations have been found with leprosy (Hatta et al., 2010), tuberculosis (Bellamy et al., 1998), rheumatoid arthritis (Ates et al., 2009), visceral leishmaniasis (Mohamed et al., 2004), multiple sclerosis (Kotze et al., 2001; Gazouli et al., 2008b), inflammatory bowel disease (Gazouli et al., 2008a; Kotlowski et al., 2008; Sechi et al., 2006) and type 1 diabetes mellitus (Paccagnini et al., 2009; Takahashi et al., 2004).

6. MAP and Type 1 diabetes

Type 1 diabetes mellitus (T1DM) is an autoimmune disease manifest by progressive T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreatic islets of Langherans (Eisenbarth, 1986). Dow in 2005 postulated a causative role for MAP in the T1DM, Sechi in 2007 found the DNA of MAP in the blood of autoimmune (type 1) patients but not non-autoimmune (type 2) diabetics (Rosu et al., 2009; Sechi, et al., 2007, 2008). Sechi also found an association of polymorphisms of the SLC11a1 gene and MAP in T1DM patients (Paccagnini et al., 2009).

While it may be intuitive to envision an occult presence of MAP as an infective agent producing a granulomatous lesion of Crohn's or sarcoidosis; it is broader divide to assign a role for MAP in T1DM. The link connecting MAP and T1DM comes from the concept of molecular mimicry: protein elements of the pathogen "look like" elements of the host to a degree that immune responses directed at the pathogen also attack the host.
One of the proposed links is the mimicry of mycobacterial heat shock protein of MAP (HSP65) and pancreatic glutamic acid decarboxylase(GAD) (Dow, 2006).

7. Molecular mimicry/ heat shock proteins - HSP65

Molecular mimicry has long been implicated as a mechanism by which microbes can induce autoimmunity (Oldstone, 1987; Raska & Weigl, 2005). Rheumatic fever is the classic example for molecular mimicry between an infecting agent—*Streptococcus pyogenes* (group A streptococcus) and a related autoimmune disease in humans (Guilherme et al., 2005; Kaplan & Svec, 1964; Kirvan et al., 2003). The disease is characterized by damage to the heart, joints, and the central nervous system (Sydenham's chorea). The activity of the host's immune system against the streptococcus generates a cross-recognition to human tissue causing an autoimmune reaction. Heart damage is the most serious consequence and is present in 30 to 45% of the cases - mostly causing damage to the heart valves.
Heat shock proteins (HSPs) are produced in response to environmental stress. They act in a protective capacity helping cells survive stressful conditions and promoting recovery (Parsell & Lindquist, 1993). During an active immune response to infection, both the host and the microorganisms synthesize HSPs. The increased expression of both self and infective stress proteins and the extensive sequence homology between microbial and human HSP (50–80% amino acid homology of mycobacterial HSP65 versus human HSP60) have led to the concept that HSPs are involved in the etiology and pathogenesis of many immune mediated disorders (Lamb & Young, 1990). Mycobacterial HSPs have been found in a myriad of autoimmune diseases (Jarjour et al., 1991). For example, the mycobacterial 65 kDa HSP has been implicated in the pathogenesis of rheumatoid arthritis (Moudgil et al.,1997; Quayle et al., 1992), autoimmune hepatitis (Miyata et al.,1995), primary biliary cirrhosis (Vilagut et al.,1997) and scleroderma (Danieli et al., 1992). HSP65 is implicated in multiple vasculitis-associated systemic autoimmune diseases such as Kawasaki disease (Yokota et al., 1993), Behcet's disease (Direskeneli & Saruhan-Direskeneli, 2003) and Takayasu's arteritis (Aggarwal et al., 1996).

8. Molecular mimicry and Type 1 diabetes mellitus

Individuals at-risk for T1DM produce anti-GAD antibodies. HSP65 was first associated with T1DM via GAD in 1990 (Jones et al., 1990). Mycobacteria produce HSP65 in response to stress. There is marked homology between mycobacterial HSP65 and human HSP60 (Jindal et al., 1989). Epitope homology between MAP/human HSP60/65 and pancreatic glutamic acid decarboxylase (GAD) likely triggers the anti-GAD antibodies that secondarily destroy the pancreas (Jones et al., 1993).
Mycobacterial HSP65 provides a well-described diabetogenic peptide, p277 (Liang et al., 2010). The critical role of immunity against hsp65 and its T-cell epitope, p277 was proven in two different experimental animal model systems: the spontaneous diabetes that develops in the diabetes model NOD (non-obese diabetic) mice, and the autoimmune diabetes induced by a very low dose of the toxin streptozotocin (STZ). Pre-diabetic NOD mice

manifest spontaneous antibody formation and T cell responses to hsp60 and to peptide p277 prior to the onset of diabetes (Birk et al., 1996; Elias et al., 1990; Elias et al., 1991). A single administration of the peptide p277 conjugated to carrier molecules can induce diabetes in C57BL/6 mice and in other strains not genetically prone to develop diabetes (Elias et al., 1995). Conversely, a single injection of unconjugated peptide p277 in NOD mice could arrest the diabetogenic autoimmune process, even when it was advanced (Elias et al., 1991; Elias & Cohen, 1994; Elias & Cohen, 1995). Additionally, administration of peptide p277 could prevent the development of autoimmune diabetes induced by very low dose of STZ in 57BL/KsJ mice strain (Elias & Cohen, 1996).

9. T1DM and milk

We now have come full circle regarding MAP, exposure to MAP, MAP in animal and human disease, epitope homology between mycobacterial HSP65 (particularly p277) and pancreatic GAD. The observation regarding risk of T1DM and early life exposure to milk warrants discussion.

Several studies indicate an association between early exposure to dietary cow's milk and an increased risk of TIDM. (Akerblom & Knip, 1998; Gerstein, 1994; Gimeno & deSouza, 1997). These studies were prompted by the observation that children at risk for TIDM who were breast fed exclusively for more than six months were less likely to have TIDM later in life than similar risk children who were weaned onto cow's milk-based formula at an earlier age. This observation spawned a large study, the TRIGR study: Trial to Reduce IDDM in the Genetically at Risk (Akerblom et al., 2010). The postulate is that there is something about cow's milk protein that is an immunologic trigger for TIDM and that breaking the protein with hydrolysis may 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. A recent, smaller but somewhat parallel study shows that exposure to the hydrolyzed infant formula resulted in lessened incidence of T1DM (Knip et al., 2010). Antibodies against specie specific MAP proteins were found in Sardinian children involved in the TRIGR study (Sechi, personal communication) As previously mentioned, viable MAP has been found in infant formula powder (Hruska et al., 2005).

10. MAP and other autoimmune disease – thyroiditis and multiple sclerosis

Two recent articles link MAP to autoimmune (Hashimoto's) thyroiditis. The same molecular mimicry principle is suggested as the link between MAP (HSP65) and the organ-specific autoantigens of thyroiditis (D'Amore et al., 2010; Sisto et al., 2010). Another recent article implicates MAP in multiple sclerosis. Molecular mimicry and SLC11A1 associations are germane here as well (Cossu et al., 2011, Gazouli et al., 2008b).

11. MAP – the future

While evidence mounts that MAP is, indeed, a zoonotic agent, what policies and interventions might be employed to address curtailing MAP and the effects of its persistence in individuals? Presently, sound farm management practices and stringent culling are

considered the best means to reduce the spread of MAP from animal to animal, as well as from farm to farm (Tavornpanich et al., 2008). However, because such practices have yet to eliminate MAP from food animals, other preventive or curative measures are needed. Industry has made an attempt to assess the risk of a positive MAP/Crohn's association (Groenendaal & Zagmutt, 2008).

TASF is a Swiss-based international forum for Transmissible Animal Diseases and Food Safety. TASF acknowledges the uncertainties of the zoonotic potential of MAP for Crohn's disease. TASF suggests that "… *a decision by food safety regulators to exercise the "precautionary principle", label MAP as a potential zoonotic agent, and adopt measures to limit as much as possible the levels of MAP contamination of raw milk and meat would go far to protect the coming generations of children from MAP exposure, possible infection, and potentially Crohn's disease.*" (TAFS, white paper, 2009).

Preliminary studies with a probiotic of the Dietzia species have been shown effective in treating clinically ill adult cows with Johne's disease and in preventing Johne's in calves (Click & VanKampen, 2009; 2010). The use of Dietzia has also been suggested for individuals with inflammatory bowel disease (Click, 2011). Vaccines are effective in reducing the incidence of clinical Johne's disease (Kormendy, 1994; van Schaik et al., 1996) and attenuate pre-existing infection (Gwozdz et al., 2000). However, such whole killed vaccines do not eliminate subclinical MAP infection or its persistence in the gut. Additionally, about half of the animals receiving whole killed MAP vaccines become false positive using the conventional tuberculin skin test diagnostic for bovine tuberculosis (Mackintosh et al., 2005; Muskens et al., 2002). DNA vaccination may have an interesting application: Sechi et al., (2006) showed that lambs vaccinated with plasmids encoding mycobacterial antigens produced a Th1 immune response similar to that generated by natural infection by MAP. Moreover, lambs vaccinated with DNA mycobacterial antigens (expecially HSP65) were protected against MAP infection. Additionally, the unfolding knowledge regarding susceptibility polymorphism of genes such as the SLC11a1 gene described in this chapter may lead to breeding practices that would limit MAP infection in breeding lines thus keeping it from the human food chain.

In humans with MAP-associated disease recognition of both the need to treat as an infectious disease as well as the need to avoid further exposure is paramount. Aggressive anti-mycobacterial treatment has had beneficial effect in those who can tolerate the treatment (Borody et al., 2007; Hermon-Taylor, 2002). Vaccines against MAP for use in humans are being advocated and prototypes are being developed (Bull et al., 2007).

12. Conclusion

The controversy regarding MAP and human disease has been going for a century and will likely continue for a long time. T1DM has only recently been added to the discussion - and controversy. In addition to the human toll to individuals with T1DM, the dollar cost is extreme; the burden is passed along to all of society in the form of higher insurance premiums and taxes, reduced earnings, and reduced standard of living. Each year T1DM costs this country $14.4 billion (11.5–17.3) in medical costs and lost income. Were the disease eliminated by therapeutic intervention, an estimated $10.6 billion (7.2–14.0) incurred by a new cohort and $422.9 billion (327.2–519.4) incurred by the existing number of T1DM patients over their lifetime would be avoided (Tao et al., 2010). This alone should elevate the discussion, draw resources and bring a sense of urgency to the MAP/T1DM connection.

13. References

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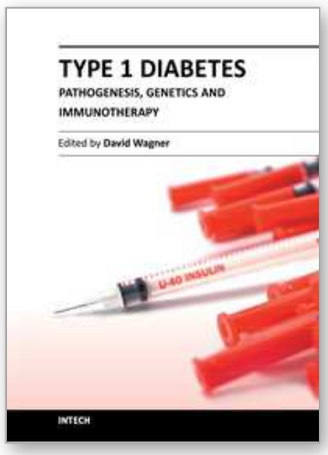

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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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