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Diabetes mellitus, tuberculosis and the mycobacteria: Two millenia of enigma

Lawrence Broxmeyer *

C/o Med-America Research, 148-14A 11th Avenue, Whitestpme, NY 11357, United States

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Summary The thought that tuberculosis and the mycobacteria could cause diabetes seems farfetched, but is not. The peculiar relationship and frequent association of diabetes mellitus and tuberculosis has been observed for more than 2000 years, yet the reason for this correlation is, to this day, not known. Before the discovery of insulin, a diagnosis of diabetes was a death sentence within 5 years, and the usual cause of that death was tuberculosis. Despite this, in the 5th century, tuberculosis was already being portrayed as a “complication” of diabetes, a view little changed to this day, parroting Root’s original 1934 description of “a one-sided relationship”: tuberculosis still seen as a common complication of diabetes, while diabetes is thought to be no more common among TB patients than in the population at large. To Nichol’s, this was “not logically tenable” and in his study of 178 otherwise healthy, *non-diabetic* military men with tuberculosis at Fitzsimmons Army Hospital, one-third had abnormal glucose screening tests. But despite his findings and those of Reaud in New York and others, this was not being recognized elsewhere, and Nichols wanted to know why. Nichols concluded that the incidence of diabetes among tuberculosis patients was considerably underestimated and that in tuberculosis patients, diabetes develops quite commonly. Diabetes was easy to detect. Tuberculosis and the mycobacteria were not.

The evidence for a mycobacterial cause of diabetes is mounting rapidly. Schwartz and Haas both linked Type-2 diabetes to tuberculosis. And the pancreatic islet amyloid deposits that they found as a by-product of systemic tubercular infection have recently been dissolved by rifampicin, a first line drug against tuberculosis. Engelbach spoke of “transitory” diabetes in TB and Karachunskii noted changes in carbohydrate metabolism in patients with tuberculosis which commonly led to insulin deficiency with persistent hyperglycemia. Furthermore, mycobacterial elements have been shown recently not only to cause “autoimmune” Type-1 diabetes in NOD (non-obese diabetic) mice, but act as a vaccine to stop the inevitable diabetes that would otherwise materialize. The documentation of patient cases where TB has preceded and come before the development of diabetes is extensive yet underplayed and both Lin’s and Tsai’s studies speak of tuberculosis complicated by diabetes. Diabetes has been around since the first century AD, in a perpetual state of coping and managing. It is time, it is long past time, to cure diabetes. But current models as to its cause are not equipping us to do so.

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Epidemic

In 1991, 2 years before The World Health Organization belatedly issued its first ever global emergency

* Tel./fax: +1 718 746 5793.

E-mail address: medamerical@cs.com.

regarding tuberculosis, a disease which is estimated to result in a human death every 10 s [1], a WHO ad hoc committee announced that an apparent epidemic of diabetes had occurred – or was occurring – in adult people throughout the world. The developing countries, as well as the minorities of disadvantaged communities in industrialized nations, particularly in the United States, seemed to be taking the brunt of it [2]. Figs. 1 and 2 are CDC maps for US Diabetes and TB, showing, in each case, a predominantly Southern US distribution for both diseases, with major inroads along much of the Eastern seaboard.

American diabetes: the Pimas

American Indians have some of the highest diabetes rates in the world, nearly four times greater than other Americans, with 40–70% of American Indian adults aged 45–74 found to have diabetes in a recent screening study in three geographic areas [3]. But it is within this subgroup, that the highest levels of diabetes in the world are found, in the Pima Indians of Arizona [4]. This drew investigators from around the world to grapple with questions such as why Pimas who chose to stay in the mountains of Mexico, away from the reservations, have such incredibly lower rates of diabetes. Although such Mexican Pimas have the “genes” for Type-2 diabetes, fewer than 1 in 15 get the disease. This argues against a genetic basis for the disease.

Diabetes, however, is not the only problem facing the American Indians and the Pimas. For if Indian diabetes soared, their rate of TB was more than five times greater than that for other Americans, most of their children becoming tuberculin-

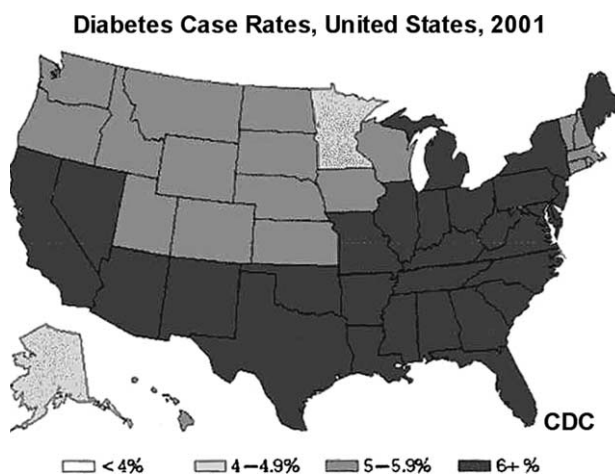


Figure 1 US Diabetes, 2001.

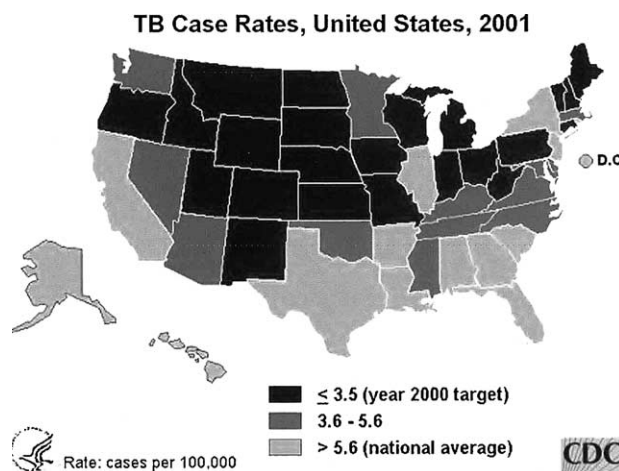


Figure 2 US Tuberculosis, 2001.

positive by the age of 10 or 15 [5]. By 1900, tuberculosis had become the most serious health problem among North American Indians [6], as well as their leading cause of infectious death [7]. And some of the most dreadful manifestations of tuberculosis susceptibility on record can be found when this group was compelled to change their ancestral ways and live on reservations [8]. The first well-documented outbreak of US Indian TB was among 2800 Sioux made US prisoners of war around 1880. Not in evidence during incarceration, soon thereafter TB deaths, in their most acute form occurred in the barracks, reaching, by 1913, Sioux mortalities at a level 10 times greater than any in Europe during the worst of its 19th century TB epidemics. And similar events were unfolding on other Indian Reservations. Runaway epidemics among North American Indians such as the Arizona Navajo and the Qu'Appelle Valley Canadian Indians left in their wake TB mortality rates of up to 9000 per 100,000, the highest anywhere at anytime. (Ibid) Despite the warm, arid Arizona climate, TB still remains the greatest cause of Navajo death, a by-product of their confinement to reservations and adopting the white man's diet and way of life.

Although tuberculosis reached the Americas with the coming of the North American Indian migrants, it only persisted at a low level of endemicity until an epidemic began 1500 years ago, thought to have originated in the Andean region of South America. Unfortunately, this epidemic did not have an opportunity to reach its apex or subside, leaving highly susceptible American Indians in the direct path of European colonizers [9]. The single worst disease present in European cities was tuberculosis and by 1800 it was understood that no other disease was as common, nor as deadly. Young noted that it caused one in four premature deaths in

England, while major Parisian hospitals simultaneously recorded 40% of their deaths as resulting from tuberculosis. This set the backdrop for a US eastern seaboard death rate of approximately 400 per 100,000 by 1830, a reservoir with which to infect the ultra-susceptible American Indians with virulent European strains.

Perhaps the most meaningful post-mortem examination of pancreatic tissue from diabetic and non-diabetic Pima Indians ever done showed that 77% of the diabetic group had amyloidosis of the islets of the pancreas compared with only 7% in non-diabetic subjects [10].

Phillip schwartz and amyloidosis

As a pathologist and lead researcher, Dr. Phillip Schwarz knew all about amyloid. But as he saw thoughts about diabetes gel into the two major 1957 categories they seemed frozen in [11]: 'auto-immune' insulin dependent (IDDM) and obesity linked non-insulin dependent (NIDDM), he also saw major flaws in the causative explanation for each. Thus when no explanation of diabetes came close to what Schwartz, in a 50 year autopsy-driven study as lead researcher uncovered for the State in Warren Pennsylvania, he published [12]. In a report of 331 autopsied cases of amyloid, ages ranging from 16 to 87, Schwartz not only showed tuberculous lesions somewhere in the body in practically all of them, usually from childhood infection, but more specifically amyloidosis of the pancreas in 224. Moreover, most of those diagnosed as diabetic prior to death showed intense islet cell amyloidosis and Schwartz hypothesized that once amyloidosis of the pancreatic islet cells hit a critical mass, the result was diabetes mellitus [12]. Thus, according to Schwartz, most cases of pancreatic amyloidosis, as well as the inflammatory infiltrate of the islet cells characteristic of Juvenile diabetes, ought to be considered an immunopathy induced by tuberculosis. Diabetes was easy enough to pick up with routine laboratory tests, TB was not, its main weapon being its insidious nature, often taking decades to discover, if then.

Schwartz knew that there were two conceivable ways in which the pancreas could be attacked by tuberculosis: First and foremost by a toxic-allergic 'immunobiologic' reaction of the pancreas in response to generalized tuberculosis, the so-called 'concomitant pancreatitis' [13]. In this case, the microbe attacks the pancreas through mycobacterial toxins and by-products dumped into the blood, resulting in both increased inflammatory susceptibility ('hypersensitivity'), and amyloidosis.

Schwartz early recognized that the fact that the microbe need not necessarily be present in pancreatic tissue would confound scientists for generations to come, leading to 'autoimmune' speculation and an inability to recognize an underlying tuberculous infection.

Pancreatic tuberculosis was thought rare by a belief that pancreatic enzymes interfered with the seeding of *M. Tuberculosis* [14]. However Schwartz considered it rather common, with tuberculous toxins and by-products leading not only to the pancreatic amyloid of adult-onset diabetes, but the inflammatory infiltration of the islet cells of the young. Such inflammatory infiltrate was recognized by Root et al. [15] to be one of the most obvious pathologic differences between juvenile and adult forms of the disease. Recently increased reporting of tuberculosis of the pancreas has supported Schwartz's findings [16].

The other, much less frequent, means of mycobacterial attack was through the direct invasion of the pancreas by either tubercle bacteria disseminated through the blood or through penetration of the pancreas by adjacent caseating abdominal lymph nodes [13]. But even in the few cases where *Mycobacterium tuberculosis* was present, it could take up to 14 weeks to grow out in the laboratory [17], a practice not routinely followed. In any scenario, Chaudhry et al. [18] concluded, a clinical diagnosis of pancreatic tuberculosis is not possible. Remarkably, Langhans' giant cells and epithelial cells, the histologic hallmarks of tuberculous infection were not evident in pancreatic tissue, just caseation leading to subsequent amyloidosis and calcification. Lazarus and Volk [19] reported that when pancreatic calcification was present there was between 23% and 50% incidence of diabetes. To further prove the connection between tuberculosis and amyloidosis Schwartz injected *M. tuberculosis* intraperitoneally into 22 guinea pigs, all of whom promptly died within 28–96 days. All but four exhibited amyloidosis. Yet only one of the control animals came down with amyloidosis [12]. With his guinea pig experiment, Schwartz supported the findings of Hass, who in a large series of rabbits, found that three out of every four animals developed amyloidosis within 15 days of being infected with bovine tuberculosis. Furthermore, the injection of tuberculin into these animals only hastened the development of amyloidosis [20].

Just as it is a well-guarded secret that glucose intolerance occurs in the setting of TB without diabetes, and is reversible following adequate anti-tuberculosis treatment [21]; so too is it glossed-over that changes in carbohydrate metabolism in patients with primary tuberculosis include an

initial, pronounced, enhanced insulin secretion leading to signs of relative insulin deficiency and persistent hyperglycemia [22]. It is just this higher secretion of insulin, leading in turn to lower functional insulin reserves, that sets the stage for the more frequent development of severe diabetes mellitus in patients with pulmonary tuberculosis. (Ibid) Moreover, such hyperglycemia, in addition to stimulating insulin hypersecretion, thru the over-stimulation of pancreatic islets to release the hormone amylin, causes just the sort of destructive pancreatic islet cell amyloidosis that Schwartz regularly documented [23].

The ultimate importance of amyloidosis of the pancreas towards the pathogenesis of age-related diabetes even shows in clinical–pathological similarities in cats and man. Thus the typical diabetic cat is obese and middle-aged, and has low but detectable circulating insulin levels. However, the most striking similarity between the species is the occurrence of islet amyloidosis (IA) in nearly all diabetic cats and in over 90% of humans with Type-2 diabetes mellitus [23]. Even before Koch discovered the causative organism of human tuberculosis in 1882, it was recognized in dogs and cats [24]. Up to 13% of cats [25] harbored the disease, often unsuspected. In addition, it soon became obvious that cats were also susceptible to *Avium* or fowl tuberculosis [26–28].

The historical roll call referenced by Schwartz of scientists linking amyloid in man and TB and the Mycobacterium is extensive and in the past amyloid's usual precipitating cause was acknowledged to be chronic infectious processes, primarily tuberculosis [29]. However, in recent years scientific thought has shifted towards non-infectious inflammatory diseases as the most commonly associated cause of amyloidosis. But, in most of these diseases, such as in the case of the inflammatory bowel diseases, there has been intensive scrutiny, thru antibody or direct bacterial evidence, to suggest that many of these diseases may indeed be of mycobacterial origin. Also, though amyloid has been found in up to 20% of these "non-infectious" diseases, such as rheumatoid arthritis, itself linked antigenically to the mycobacteria [30], such amyloid is only clinically significant in 3–5% of cases [29]. Meantime, studying the autopsy findings in cases of the so-called "primary" or non-infectious amyloid reported in the literature, Schwartz [12] found important omissions in ruling out the possible presence of active or inactive tuberculosis, never stated and never looked for.

By 1994, de Beer and Nel [31], studying the relationship between a major rise of serum amyloid, and having tuberculosis, saw a rapid descent in

amyloid levels in patients treated with anti-tubercular drugs. Tomiyama and Asano [32] dissolved beta-amyloid plaque with rifampin, a first line drug for TB, and one of the few agents, to this day, that is able to dissolve Alzheimer's plaque. In November 2004, a study by Anthony Fink out of the University of California, Santa Cruz, appeared in *Chemistry and Biology* which although it dissolved protein aggregation in the brain of Parkinson's patients, was linked, in an accompanying editorial by Kapurnictu, to similar molecular events in Alzheimer's, Mad Cow Disease and even Type-2 diabetes. Fink also used Rifampin to dissolve the protein aggregates. Livingston and Alexander-Jackson [33] consistently found acid-fast germs in Wilson's disease, a primary cause of Parkinson's in the young. Indeed, striking parallels between the pathogenesis of islet amyloidosis in diabetes and beta-amyloid plaque formation in Alzheimer's disease [23] and in his 50 year study, based upon autopsy, Schwartz saw amyloid degeneration and a focus of tuberculosis, usually from earlier disease, in just about every case of Alzheimer's and Diabetes [12].

The science of denial

Before the discovery of insulin, a diagnosis of diabetes was a death sentence with which the average person lived less than 5 years after diagnosis, and the usual cause of death was tuberculosis. A century ago diabetics were virtually doomed to die of tuberculosis if not fatal diabetic ketoacidosis [34]. Root, in reviewing the history of the association of diabetes and tuberculosis, noted that "in the latter half of the 19th century the diabetic patient appeared doomed to die of pulmonary tuberculosis if he succeeded in escaping coma". In 1883, Bouchardat stated "at autopsy every case of diabetes had tubercles in the lungs" [35].

Root presented an interesting analysis of 1121 autopsied diabetics in 1934, from which he concluded that active tuberculosis occurred two to three times more frequently than expected [36]. But because in studies like Root's diabetes seemed to usually precede tuberculosis, it was concluded that the 5th century notion [37] that diabetes came first, and with it a weakness towards contracting and dying from TB later, was valid. To Nichols [38], this came from a "peculiar consensus", which "did not seem proper". Even Munkner [39] objected to Root's conclusions, writing that one would expect a somewhat increased number of diabetics within a group of tuberculosis patients as well. Yet it was Root's [36] 1934 "one-sided association" between TB and diabetes, that others

would blindly follow to this day. To Nichols though, it was not a question of whether diabetes developed commonly in TB patients. He knew it did. Rather Root and others had gone wrong simply through the fact that the early detection for diabetes was far, far better than that for tuberculosis and the mycobacteria.

Certainly in his paper, Root's "remarkable cases" point more towards Nichol's views than his own. Root's case with a 5-year-old boy, who, one year after his grandfather's untimely death (with whom he lived) from pulmonary tuberculosis came down with juvenile diabetes seemed questionable. Only at the age of 12, when the boy already had extensive disease, did pulmonary tuberculosis reveal itself, but the disease could have been easily transmitted to him prior to his diabetes [36]. Another of Root's "remarkable" cases cites a 15-year-old female who developed TB first, only to come down with diabetes, diagnosed in the Massachusetts General Hospital, 7 years later [36]. This was followed by a 30-year-old female with active pulmonary TB who subsequently came down with diabetes at the age of 45, 15 years later. (Ibid) Were Root and others ignoring the obvious?

The documentation of cases in patients with TB having preceded and originating before the development of diabetes is extensive yet underplayed [40–42]. Studies by both Lin and Tsai spoke of tuberculosis complicated by diabetes rather than the other way around [42,43], finding diabetes more prevalent among TB patients in urban areas. Not only did glucose intolerance occur in the setting of TB without diabetes, reversible following adequate anti-tuberculosis treatment [21], but pulmonary resection for tuberculosis in patients with severe diabetes mellitus reduced the severity of their diabetes [44]. Engelbach [45] spoke of "transitory" diabetes in some of his TB patients prior to treatment.

By 1990, a landmark article appeared in the February issue of the respected *Proceedings of The National Academy of Science*. Elias and Markovits had carefully laid out their case. Insulin-dependent juvenile diabetes, all along thought to be from "autoimmune" destruction of the insulin-producing pancreatic islet beta cells, had been shown to be caused, in mice, by an antigen cross-reactive and therefore related to a heat shock protein found in *Mycobacteria tuberculosis* [46]. All organisms and all bacteria have the ability to produce heat shock proteins, abbreviated HSP, as a survival strategy involving thermoprotection against temperature extremes which could otherwise kill them. Heat shock protein 70 (HSP-70) in fact has

been found in every bacteria and organism it has been looked for, but not so for HSP-65, a tuberculosis and mycobacterial heat shock protein which happens to be a member of the HSP-60 heat shock protein family. In their study, Elias and Markovits actually saw the onset of beta-cell destruction occur from lymphocytes developed to destroy and rid the body of these mycobacterial elements, heat shock protein 65 (HSP-65), a phenomena which did not occur when HSP-70, common to all bacteria, was used. Some weeks later antibodies to these HSP-65 of tuberculosis also formed, along with anti-insulin antibodies. And as all of these began to decline, overt insulin-dependent diabetes developed.

The importance of these mycobacterial elements of tuberculosis was confirmed by their instigation of insulinitis (inflammation of the pancreatic islet cells) and hyperglycemia in just the kind of non-obese mice most prone to developing spontaneous, "autoimmune" insulin-dependent diabetes mellitus. Moreover, infection of these animals with tuberculosis or some of the other mycobacteria, or immunization with certain mycobacteria-containing adjuvant resulted in permanent protection of these very same mice from diabetes [47]. The researchers therefore concluded that the HSP-65 manufactured by *Mycobacterium tuberculosis* could not only be used to induce diabetes but to serve as a vaccine against it. (Ibid) This was direct laboratory evidence that tuberculosis could indeed cause or prevent diabetes, and it was not alone. Studies showing the prevention of diabetes in similar non-obese diabetic (NOD) mice otherwise destined to spontaneously develop the disease soon came in regarding other mycobacteria, such as *Mycobacteria bovis* or bovine tuberculosis [48], *Mycobacterium avium* or fowl tuberculosis [49] and even *Mycobacterium leprosy* [50]. But the possible causative responsibility of the mycobacteria in diabetes was still being all but ignored.

Conclusion

In 1995, the number of adults with diabetes mellitus was estimated to be 135 million worldwide; this number is expected to increase to 300 million by 2025. Diabetes has been around since the first century AD in a perpetual state of coping and managing. It is time, it is long past time, to cure diabetes. Schwartz and Haas's studies, linking diabetes, tuberculosis and the mycobacteria, laid the foundation for such a cure and a series of studies done only within the last decade or two further solidify that link. Nichols [38] stated outright that

on the basis of his evaluation that diabetes, where it looked for, should be quite common in tuberculosis patients. The problem is, it never has been. Thus while mankind continued its struggle to come to grips with the cause and thereby win the war against diabetes, tuberculosis and the mycobacteria continue their silent destructive path towards causing it, unobstructed by the advance of science.

Engelbach [45] spoke of “transitory” diabetes in some of his TB patients prior to treatment. Perhaps the best kept secret among the traditionalists is that just as glucose intolerance occurs in the setting of TB without diabetes [21], changes in carbohydrate metabolism during primary tuberculosis also lead to enhanced insulin secretion and eventual signs of relative insulin deficiency with persistent hyperglycemia, a predecessor to the severe diabetes that follows [22]. Moreover, such hyperglycemia also, thru over-stimulation of the pancreatic islet hormone amylin (also known as IAPP or islet amyloid polypeptide) instigates just the kind of destructive pancreatic islet cell amyloidosis Schwartz documented regularly [23]. Recently, specific tuberculosis and mycobacterial proteins have been shown to directly cause insulinitis, hyperglycemia and diabetes in mice thru the production of anti-insulin antibodies [46], in just the sort of manner that many would interpret as the “autoimmune” destruction of pancreatic islets in Type-1 diabetes. The problem is, there’s nothing “autoimmune” about the process other than the fact that you cannot recover the actual bacteria doing the damage against target pancreatic tissue.

That there is nothing regarding the current theory of diabetes that is set in stone has recently come to our attention. Presently under scrutiny are the long-relished, age-based categories, only first differentiated in 1957 [11], insisting that the vast majority of children and teenagers had Type-1 diabetes (“insulin dependent” or “IDDM”) — a lifelong problem which occurred when cells in the pancreas failed to produce insulin, the controller of blood sugar. In contrast, experts saw Type-2 diabetes (non-insulin dependent or NIDDM) as a disease primarily of the middle-aged and elderly who no longer responded properly to insulin and had some pancreatic failure.

But, the lines between these 1957 age categories are crumbling, swiftly. If, in the US, you are now diagnosed with diabetes in your late teens or early 20’s, you are more likely to have Type-2 diabetes than Type-1. Moreover, although this increasing prevalence of Type-2 diabetes in US children is mostly in minority groups, it is fast gaining a foothold in non-minority children as well [51,52]. And the same holds true in the UK where the child

or adolescent need not be in a minority group to have Type-2.

Although it is conceivable that a complete eradication of tuberculosis and related mycobacteria might prevent diabetes mellitus of the aging and perhaps young, Schwartz preferred to leave this question open to further investigations by other authors. However such studies, although they have appeared in limited numbers and are supportive, have come at what for diabetics has been a painfully slow rate.

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