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The Streetlight Effect in Type 1 Diabetes

In the nearly 100 years since the discovery of therapeutic insulin, significant research efforts have been directed at finding the underlying cause of type 1 diabetes (T1D) and developing a "cure" for the disease. While progress has clearly been made toward each of these goals, neither vision has been fulfilled. With increasing pressure from both public and private funders of diabetes research, growing impatience of those with T1D at the lack of practical discoveries, increased competition for research funds, uncertainties on the reproducibility of published scientific data, and questions regarding the value of animal models, the current research environment has become extraordinarily difficult to traverse from the perspective of investigators. As a result, there is an increasing pressure toward performance of what might be considered "safe" research, where the aim is to affirm existing dogmas rather than to pioneer efforts involving unconventional thought. Psychologists refer to this practice as "observational bias" while cartoonists label the process the "streetlight effect." In this Perspective, we consider notions in T1D research that should be subject to bold question and provide additional concepts, many somewhat orphan to research efforts, whose investigation could lead to a means for truly identifying the cause of and a cure for T1D.

THE STREETLIGHT EFFECT

The historical origins for the notion of the "streetlight effect" are subject to considerable debate (https://en.wikipedia.org/wiki/Streetlight_effect). Regardless, perhaps its most famous use was an application within the comic strip *Mutt & Jeff* (1) (Fig. 1). The narrative ascribed to this streetlight effect conveyed a message:

> A police officer is patrolling a neighborhood when he sees a man, disheveled and reeking of alcohol, crawling around underneath a streetlight. The officer walks over to the man and asks if there is a problem. The

drunkard turns to the officer and conveys that he dropped a quarter and was trying to find it. The officer peruses the area and after observing nothing in the light emanating from the streetlight, he asks the man where exactly he dropped it. With this, the drunken man replies that he dropped it two blocks away. When the police officer asks him why he is looking for his money all the way over here, the man replies, "Because the light is better here."

WHY MIGHT THE MORAL BE RELEVANT TO TYPE 1 DIABETES RESEARCH?

In our own considerations of the messages resident in this comic strip, we see profound analogies with the past and, sadly, much of the current state of affairs with respect to type 1 diabetes (T1D) research. To be clear, the vast majority of research efforts in T1D have—and continue to be undertaken with—a notion akin to the quarter is lost (i.e., a need to understand the pathogenesis of this disease is worthy of efficient discovery) and worth finding (i.e., a means to prevent and cure T1D is desperately needed). However, our fear is that the predominant moral of this story has been effectively lost on far too many and with increasing frequency in the T1D research community.

The reasons for our collective and generalized failure to explore research areas subject to limited or no light are many. Among the most predominant, exploration in the dark is difficult. Indeed, the rewards of academic research (e.g., publications, grant funding, promotions) appear far more often dispensed to those that find ways of producing efforts within the light that appear to be appropriate and within an effective course of action (i.e., confirming existing theories, affirming conventional wisdom, bolstering dogma, providing incremental advances) but not necessarily to those willing to take the risk to find the lost quarter no matter the location and make true, meaningful discoveries. In defense of

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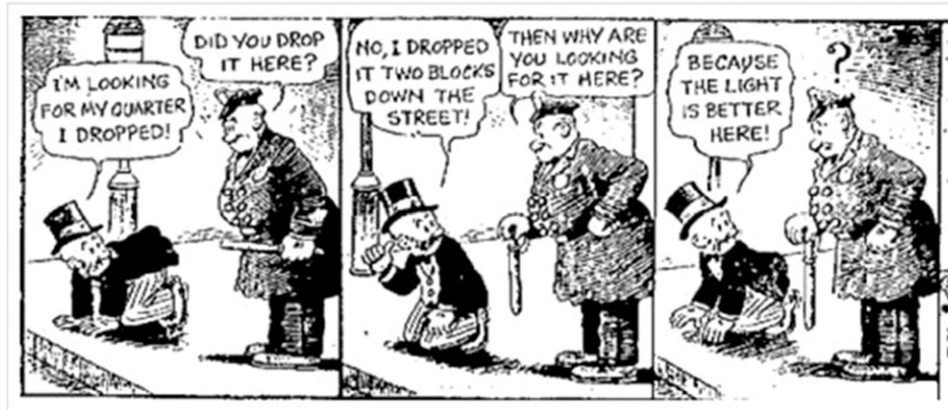Corresponding author: Mark A. Atkinson, atkinson@ufl.edu.

Figure 1—The streetlight effect. In June 1942, a version of the streetlight effect appeared in a popular syndicated comic strip, *Mutt & Jeff*. Three of the five panels in the strip are shown. The gentleman in the top hat is Jeff, and in the final omitted panel the officer joins Jeff in the search beneath the streetlight (1).

researchers in the field of T1D, one could say that, for instance, studies of the etiology and pathogenesis of this disease were not possible until the advent of improved technologies and trials that allow studying children at increased genetic risk or access to organ donors with T1D. Nevertheless, we believe we all suffer, to a certain extent, from the streetlight effect as "observational bias"; in other words, we like to study what has been and likely will continue to be observed. This situation is, however, quite ironic to those who take a risk and explore the dark, thus providing truly innovative and transformative information. The term "streetlight effect" adopted in this Perspective refers to the trend in T1D research of looking where it is convenient and easier to look. This observational bias excludes the notion of "looking in the wrong place at the wrong time," though this is undoubtedly at times the case in T1D research.

A CRITICAL AND TRANSPARENT EVALUATION OF THE PROGRESS IN UNDERSTANDING THE IMMUNOPATHOGENESIS OF T1D—A POTENTIAL STREETLIGHT EFFECT EXAMPLE?

In 1963, Mackay and Burnet (2) defined autoimmune disease as "a condition in which structural or functional damage is produced by the action of immunologically competent cells or antibodies against normal components of the body" and that arose by "the emergence of forbidden clones" of lymphocytes. That monograph listed many common autoimmune disorders; however, among the notable omissions from the list was T1D. In 1992, Ian Mackay, Burnet's lifelong colleague, published a process diagram of an immune (and presumably an autoimmune) response (Fig. 2A). McKay's comment on the diagram is quite apposite:

> Note how this stands in contrast to the limited knowledge base available to Burnet in the 1950's. Some of these discoveries would hardly have been

dreamt of by Burnet, but he would have surely applauded them. Others were clearly predicted in his writings (3).

Those noteworthy discoveries (Fig. 2A) included antigen presentation by specialized phagocytic cells in association with MHC molecules; the genetic processes that determine the structure of antibody molecules; B- and T-cell receptors for antigens; functional subsets of T cells; activation molecules on the lymphocyte surface and their influence on cellular trafficking; immunoregulatory circuits involving antigen, T, and B cells; cytokine networks; the mode of participation for B cells, T cells, and cytokines in the effector phases of immune and autoimmune responses; and so on. Remarkably, the exact same events and immune players are still depicted today as predominant facets when we describe the immunopathogenesis of T1D (4) (Fig. 2B).

Clearly, new findings suggest that the immunological picture might be more complex than that previously imagined. However, we believe that an active effort exists to maintain a "simple" picture of T1D pathogenesis—one that is highly T-cell centered—thus forming our first facet we believe is a streetlight example.

WHAT NOTIONS IN T1D RESEARCH REPRESENT EXAMPLES OF THE STREETLIGHT EFFECT?

Streetlight #1—T1D Is a T-Cell–Mediated Disease
Current conventional wisdom portrays T1D as a T-cell–mediated autoimmune disease that leads to the specific destruction of pancreatic insulin-producing β-cells. With this notion, a "triggering" insult leads to the recruitment of antigen-presenting cells (APCs), which pick up self-antigens released by injured β-cells and transport them to the pancreatic lymph nodes for presentation to autoreactive T cells. This is followed by migration to the islets of these activated self-reacting T cells, which mediate β-cell killing and promote further inflammation (reviewed
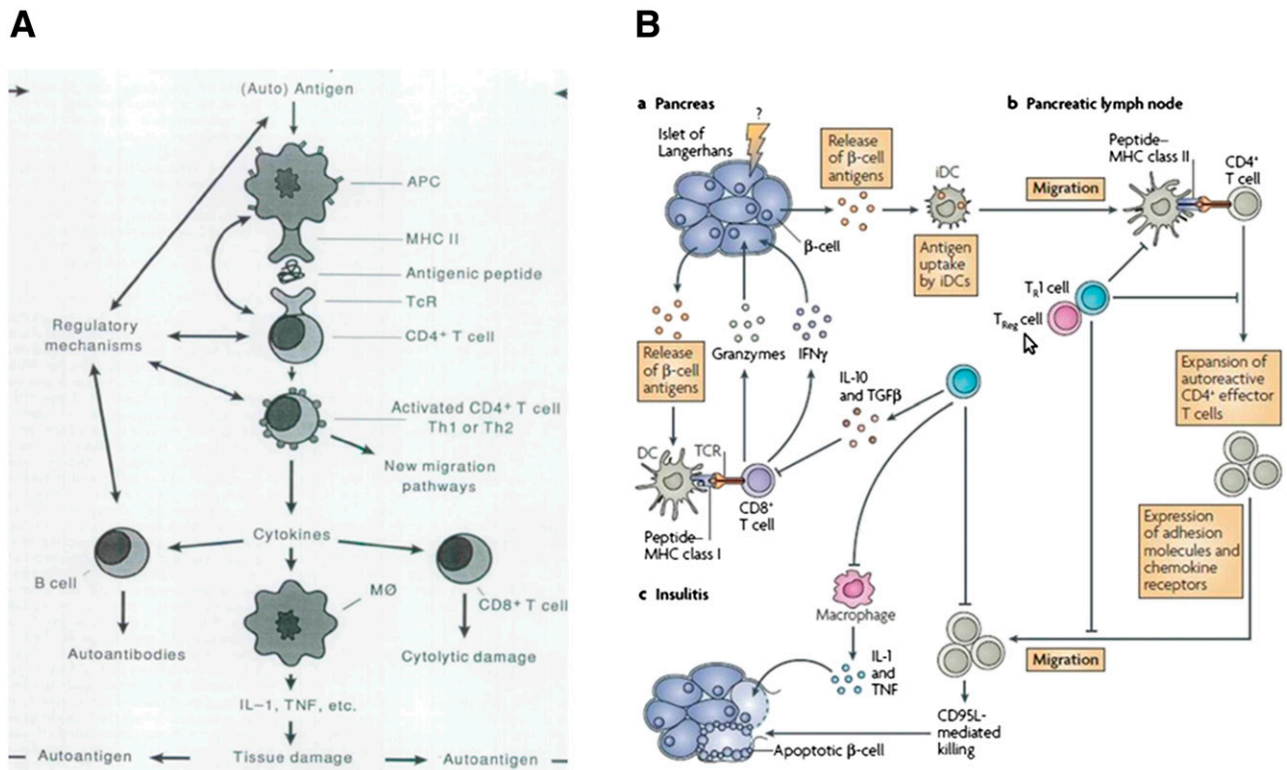
Figure 2—The pathogenic basis of β-cell destruction in T1D. Shown are models ascribing the key immunological facets relevant to the destruction of β-cells that result in T1D, considered contemporaneous "state of the art," based on established literature in (A) 1992 and (B) 2007. Reproduced from Mackay (3) and Roncarolo and Battaglia (4), with permission.

in 5). While forming current dogma, we are disappointed as to how the collective us, a community of researchers, has advanced this concept or considered other potential contributing factors to the pathogenesis of the disease.

Among the many factors underrepresented in the considerations of T1D immunology (Fig. 3) are those of innate immunity and inflammation, facets that have been repeatedly tied to T1D development (6). Indeed, among the many constituents that participate in disease formation, neutrophils are likely to play a key role. A reduced number of circulating neutrophils in subjects at increased risk for T1D as well as in patients with established disease has recently been reported (7). Beyond this, neutrophils reportedly infiltrate the pancreas of patients with T1D but not those of subjects without diabetes (7). Preclinical findings in the NOD mouse model of T1D also support the pathogenic role for neutrophils in disease initiation, as do plasmacytoid dendritic cells (pDCs) and B1 cells (8). pDCs have also been documented as abnormal in patients with T1D (9,10). More recently, type I interferon overproduction has been described as a valid biomarker in the prediction of T1D (11,12).

An additional, largely neglected immune cell subset in T1D is γ-δ (γδ) T lymphocytes. In the NOD mouse, interleukin-17$^+$ γδ T cells are essential effectors in T1D

development (13), while in humans data are scarce, old, and contradictory (reviewed in 14). This example of γ-δ T cells is typical of research areas that address cells rarely circulating and largely found in the tissue. Thus, the new availability of relevant tissues from patients with T1D and control subjects, such as those emanating from the Network for Pancreatic Organ Donors with Diabetes (nPOD) (15), should foster research aimed at not only confirming old hypotheses but also testing new ideas.

Space constraints limit us from discussing the full cadre of potential constituents of inflammation and the innate and adaptive immune responses that likely contribute to the disorder's pathogenesis. Nonetheless, their evaluation largely resides outside of the streetlight and, hence, represents an important venue for expanded exploration.

Streetlight #2—T1D Is a Disease With Specificity for β-Cells

The streetlight has been quite alluring for those investigators addressing T1D from the perspective that the disease is one largely restricted to the pancreatic endocrine compartment, especially β-cells. This is, perhaps, among the most perplexing and "obfuscated" of the streetlight effects as studies dating back to the 1940s have shown patients with T1D possess abnormal exocrine

Immune Mechanisms	Exocrine Pancreas	"Normal" Pancreas & β-Cells	Heterogeneity of T1D

• Innate immunity
• Inflammation
• Cellular phenotypes
  • Neutrophils
  • Plasmacytoid DC
  • B1 cells
  • γδ T cells
• Exocrine pancreatic infiltrate
	• Exocrine insufficiency
	• Acinar atrophy
	• Exocrine autoimmunity
	• Neutrophil inflammation
	• C4d deposition
		• Pancreas size
		• Number of β-cells at birth, childhood, adolescence
		• Exocrine function
		• β-cell remodeling
			• Pancreatic pathology
			• Age at onset (< or > 15 years)
			• Variable:
			  • Periods of autoimmunity
			• Genetic susceptibility
			• Loss of β-cell function

Commonalities in T1D & T2D	β-Cell Loss/ Function	Insulitis	β-Cell Mass at Onset
• Immunological features • Obesity • Insulin resistance • Pancreatic pathology • Genetics	• β-cell preservation • Small clusters & single cells • Pseudoatrophic islets • Islet heterogeneity	• Lobular nature • Focal distribution • Distinct quantitative & qualitative features • Peak near disease onset (?)	• Quantitative heterogeneity at onset • Dysfunctional islets • Empty β-cells (?) • Qualitative heterogeneity over time

Figure 3—Underinvestigated areas of T1D research due to the streetlight effect. At least eight features, be they pathogenic, immunologic, physiologic, or metabolic, appear to be misunderstood or underappreciated in T1D. The features described within these domains form key areas for research moving forward, when attempting to understand the pathogenesis of this disorder.

pancreatic tissue (16), subclinical exocrine insufficiency (17), and acinar atrophy (18).

It is, however, still unclear whether the exocrine dysfunction (Fig. 4) in T1D amounts to primary or secondary damage caused by the pathogenic events that also lead to islet destruction and loss of β-cells. Studies in animal models suggest that insulin deficiency affects the survival of acinar cells and the synthesis of certain pancreatic enzymes (19). However, the presence of residual insulin-producing cells in patients with T1D does not correlate with the degree of acinar atrophy (20). Hence, while it is generally accepted that insulin plays a role in acinar atrophy, it does not always correlate with a lack of insulin-producing β-cells. Beyond this, several studies have reported the occurrence of autoantibodies to exocrine antigens (e.g., carbonic anhydrase II [21], lactoferrin [22], bile salt-dependent lipase, and pancreatic cytokeratin [23]). We recently measured the complement degradation product, C4d, in pancreata from patients with T1D, type 2 diabetes (T2D), and T1D autoantibody-positive and T1D autoantibody-negative subjects (i.e., control subjects). Median total pancreatic C4d antigen density was highest in patients with T1D (24). We have also demonstrated that neutrophils infiltrating the pancreatic parenchyma of patients with T1D are primarily observed in the vicinity of acinar cells (7). These data were

recently confirmed by an additional study showing enhanced levels of CD4$^+$, CD8$^+$, and CD11c$^+$ cells in the exocrine tissue of patients with T1D (25).

Thus, in contrast with the thorough documentation and repeated discussion of autoimmunity against pancreatic islets in patients with T1D, these findings suggest that the pancreatic immune attack is not β-cell specific. Very little attention has been accorded toward investigation of autoimmune responses to, and the dysfunction of, the exocrine pancreas in T1D, forming an obvious area for additional research.

Streetlight #3—Insulitis Is a "Hallmark Lesion" in T1D

A limited number of reports dating back to 1902 has examined pancreatic specimens from people with what we now refer to as T1D; however, the effort most often considered seminal was published by Gepts in 1965 (18). This work was consistent with historical efforts in noting that a reduction of β-cells occurs in T1D along with the presence of an inflammatory infiltrate of islet cells, now commonly termed insulitis. Insulitis is often used as one of a triad of evidences, alongside anti-islet cell autoantibodies and genetic susceptibility associated with HLA, that coalesce to support an autoimmune nature for T1D (26). Given the difficulty of obtaining human pancreatic specimens, studies in the era
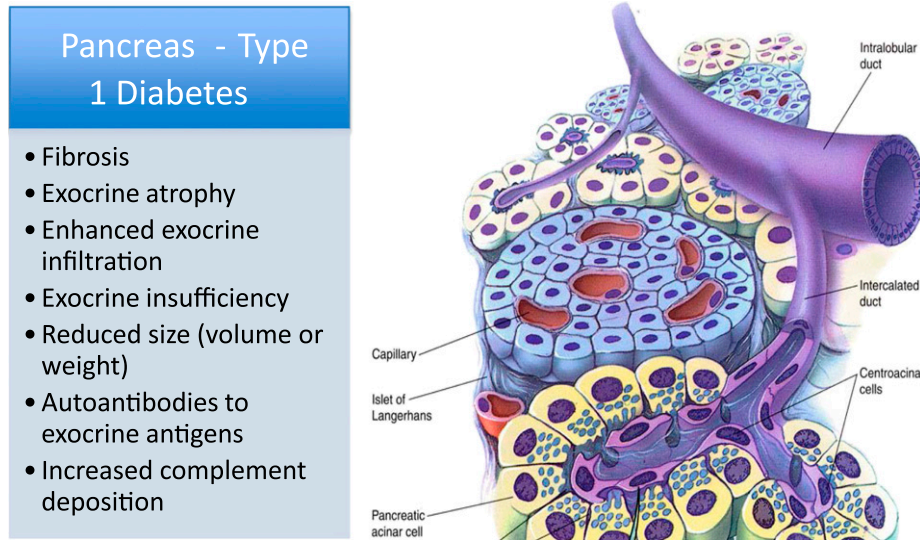
Pancreas - Type 1 Diabetes

- Fibrosis
- Exocrine atrophy
- Enhanced exocrine infiltration
- Exocrine insufficiency
- Reduced size (volume or weight)
- Autoantibodies to exocrine antigens
- Increased complement deposition

Figure 4—Key physiological features, with varying degrees of distinctiveness, that have potential relevance to the pathogenesis of T1D. Indicated (insert) are facets that have been ascribed to the pancreas in T1D, with key anatomical features noted within the illustration. Figure adapted, with permission, from the Yale University Office of Digital Dissemination.

since have been quite limited, and as a result, much of our understanding and popular description of insulitis derive from studies of NOD mice. In that animal model of T1D, insulitis has become its own form of experimental hallmark, alongside that of disease incidence. Thus, for reasons of availability and the utility of animal models, at least three streetlight notions reign predominantly in T1D regarding the features of insulitis.

First, there is a common belief that the insulitis lesion is a relatively widespread if not universal feature of the disease. The reasons for this are quite perplexing in that in the original study by Gepts (18), nearly a third of the subjects demonstrated no such pathology; a finding confirmed in subsequent investigation (27). One can only presume that a major contributing factor resides with analysis of the pancreas of NOD mice, where T1D does not occur without insulitis (28). A second feature subject to misunderstanding pertains to both the quantitative and qualitative features of insulitis. In terms of the quantity of inflammatory cells, historically, no universally recognized definition of insulitis existed. In fact, the definition used has been quite heterogeneous in the literature (e.g., 2, 3, 5, 15 infiltrating cells/islet). As a result of this, an expert panel assembled by the nPOD has recently attempted to rectify this situation through a provision of a definition of insulitis: "The lesion should be established in a minimum of three islets, with a threshold level of $\geq$15 CD45$^+$ cells/islet before the diagnosis can be made" (29). Hence, quantitatively, insulitis is in fact quite minimal. With respect to qualitative features, within a given pancreas, near the time of clinical presentation, there are islets where the β-cells have been destroyed, islets where β-cells are being destroyed,

and islets where the β-cells have yet to be destroyed (i.e., insulin-deficient islets, inflamed islets, and normal islets, respectively).

With this evidence, it is clear that insulitis in T1D represents quite a variable response, subject to marked heterogeneity in both the degree as well as the patterns of destruction. Clearly, additional studies outside of the streetlight are required to define its role in the natural history of β-cell destruction in T1D.

Streetlight #4—T1D Develops When 85–95% of β-Cells Are Lost

Be it in the introduction of an article pertaining to the pathogenesis of T1D or a sentence conveyed to the newly diagnosed patient and their family, the notion that the symptomatic onset of the disease occurs when 85–95% of the β-cells have been destroyed is one of the most oft-repeated pieces of prose in reference to T1D. Evidence in support of this notion is, however, surprisingly limited.

Pathological examinations would suggest that clinical presentation occurs when approximately two-thirds of the islets are insulin deficient, but the range is quite variable (30). Indeed, the degree of β-cell loss at symptomatic onset appears dependent on a number of factors (e.g., age, degree of β-cell dysfunction, insulin resistance), consistent with previous discussions on differences between the pancreata of those diagnosed with T1D less than or greater than 15 years of age (27). Beyond this, the pancreas before, at, and for a few years after clinical presentation may be qualitatively similar, with all three types of islet present (i.e., insulin-deficient islets, inflamed islets, and normal islets), although in vastly variable proportions (30). This becomes important in that it affords

a notion whereby the pathogenesis of T1D within the pancreas in reality likely involves progression along one of two pathways, each representing a form of the classic chicken-and-egg scenario, that takes a normal insulin-containing islet to a pseudoatrophic form (i.e., devoid of insulin). Whether or not islet inflammation of an otherwise healthy β-cell comes first or whether alterations in β-cell function or form drive inflammation in human T1D remains unknown. This, as suggested in both pathways, appears to be present in cases subject to recent examination (31).

Streetlight #5—In Early Life, the Pancreas in T1D Is Normal, With β-Cell Autoimmunity Marking the Initial Pathogenic Step in the Disease Process

In the most widely recognized natural history model for T1D (Fig. 5), the β-cell mass has limited quantitation with a notion of "100%" assigned for the beginning of life (32). In combination with this, a consensus exists that the so-called normal adult pancreas possesses approximately 1 million islet cells (33). These concepts have drawn little attention or question over time, as much of the research interest in terms of the disorder's natural history has focused on genetic susceptibility and the trigger period, where the 100% β-cells begin a process of linear loss. However, a limited body of largely unnoticed data draws into question the notions of a normal pancreas as well as the number of islets and/or β-cells that may be resident in early life through adulthood in humans.

Many years ago, both ultrasound and autopsy studies examining people with T1D noted reduced pancreatic weights in patients with long-standing disease (34). In the years since, the observation drew little investigator attention, with an overriding notion that lack of insulin, a growth factor, would over time lead to exocrine atrophy.

However, recent studies assessing pancreatic volume in living patients with T1D using noninvasive radiology methods (35) or through examination of pancreatic weights from organ donors with or at increased risk (i.e., autoantibody-positive) for T1D (36) suggest the notion of a "small pancreas" not only exists at disease onset but perhaps predates symptomatic disease. Taken collectively, these studies suggest pancreatic weights and volumes are reduced by 20–50% in patients with overt disease and in individuals at high risk. Whether this reflects a reduced pancreas volume also at birth remains only an interesting, and still unexplored, hypothesis. The reduction in pancreatic weight and volume in T1D largely represents a loss of exocrine tissue as islets constitute only 1–2% of the pancreatic mass (33). In support of this concept, a decline in exocrine function, as measured by stool chymotrypsin and elastase, has been noted (37).

The situation becomes even more intellectually diffuse when one considers the quantification of islet and/or β-cell numbers. In studies of pancreatic development in both humans and rodents, it appears that a wave of β-cell death occurs as a normal physiological process following birth (38). This may express itself physiologically as the cause of hyperinsulinemia noted to occur in early infants (39). Indeed, histological examinations of rodent pancreata assessing the frequency of dying cells suggest that up to one-third of β-cells turn over during this early period of development (40). The implications for this process may influence T1D pathogenesis in at least two ways.

First, it has been hypothesized that an early "priming" event in the pathogenesis of T1D involves the uptake of β-cell antigens by APCs due to naturally occurring β-cell death. The APCs harboring β-cell antigens would migrate from the islets to pancreatic lymph nodes where
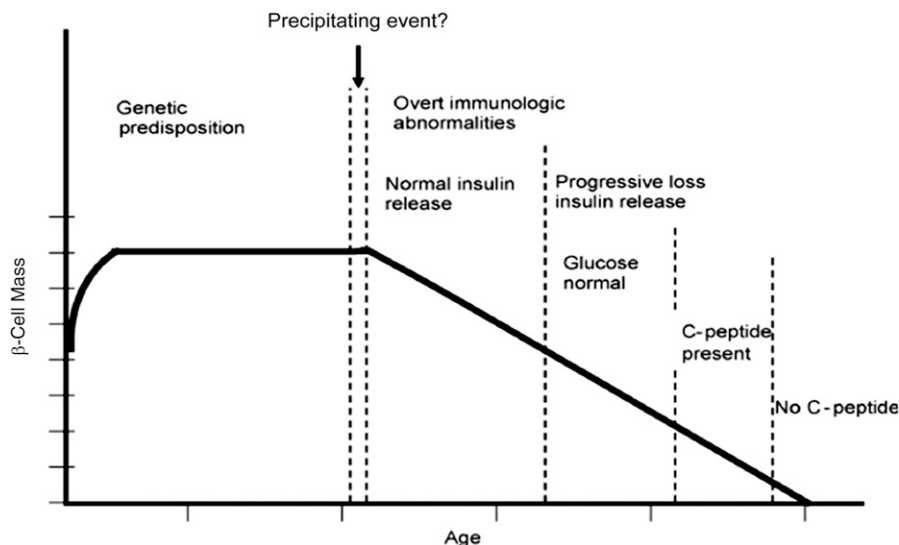

Figure 5—The "classic" model ascribing the natural history of what we now refer to as T1D. Reproduced from Atkinson et al. (26), with permission.

presentation to autoreactive T cells would occur (41). In support of this, studies of fetal and neonatal human pancreata suggested that widespread infiltrations of the exocrine pancreas with APCs, as well as T cells, are normal features in the developing pancreas (42). While certainly an interesting and highly plausible model well supported by data extracted from studies of animal models, its application to human T1D remains theoretical as current methods allowing for safe testing of this notion in vivo and evidence from human pancreatic tissues are lacking.

However, we would posit a second notion as being of equivalent, if not an even greater, potential—one relating to the aforementioned concept of "100%" (32). While data quantifying the absolute number of β-cells in childhood and adolescence are minimal in healthy individuals, recent information in adults is quite striking if not surprising. Those efforts suggest that in nondiabetic populations over the age of 20 years, the β-cell mass (g/kg) varies from 0.4 to 4% of the pancreatic weight (i.e., a log-fold variation) (43). Hence, given that β-cell replication after the age of 10 years appears rare (44), the number of these cells is likely "fixed." Hence, it is conceivable that a major and yet highly unappreciated risk factor for T1D resides in the number of β-cells present in early life (Fig. 6). While the processes underlying regulation of β-cell

remodeling are unknown, they may be related to nutrition, stress, microbiome, or other as-yet unidentified reasons. These explanations were developed based on concepts that the weaning period represents a developmental stage marked by a pronounced change of metabolic processes as well as hormone production (45). Furthermore, during development, a variety of tissues beyond those of pancreatic islets undergo a process of remodeling marked by cellular apoptosis and/or necrosis. Indeed, both processes may go hand in hand as the physiological changes due to weaning may signal the process of tissue remodeling.

Taken collectively, these findings support a hypothesis that immune and perhaps nonautoimmune mechanisms (e.g., developmental, environmental, genetic) influence a loss of β-cell mass as well as loss of pancreatic mass in T1D, possibly even before full-blown disease, thus forming clear objectives for future studies.

Streetlight #6—Over Time, People With T1D Have a Complete Loss in the Ability to Produce C-Peptide, Reflecting a Complete Loss of β-Cells

Of the streetlights noted in this Perspective, this is perhaps the one where recently there has been some willingness of investigators to migrate from the light, yet more of such actions are needed. Based in large part
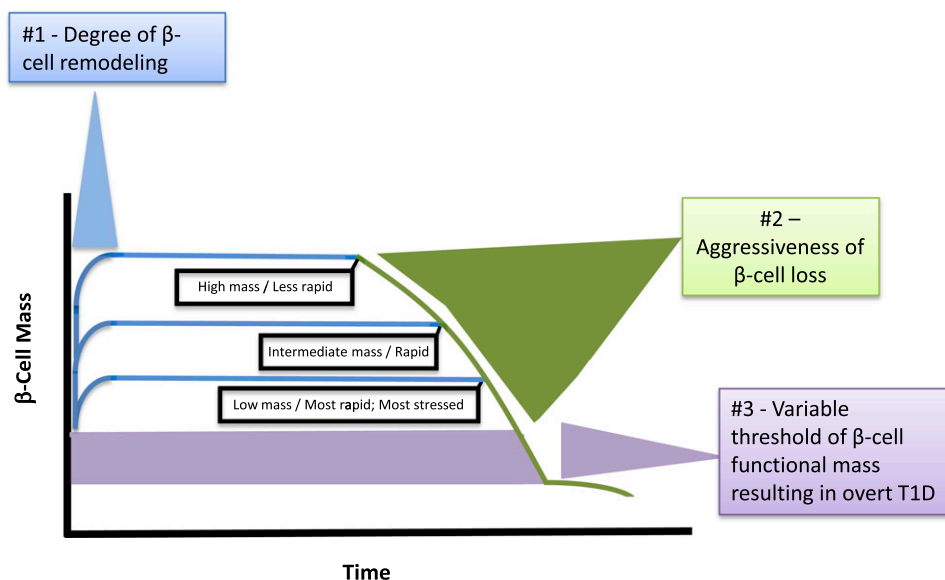

Figure 6—Three key facets of β-cells relevant to the pathogenesis of T1D. Based on a growing body of literature, the quantity of β-cell mass present in early life (i.e., first 1–2 years) is a potential early indicator of both the risk for T1D as well as the time to disease onset. A second feature, the aggressiveness of β-cell loss, is a notion influenced by a combination of genetically or environmentally driven susceptibility of β-cells to their demise, their functional activity, and their resistance to destructive efforts imparted by the immune system. The third facet is that of the mass of β-cells required to avert the symptomatic onset of T1D. Rather than the classic "fixed percentage" so often thought of (i.e., 85–95%), a relatively wide range is a far more likely scenario, influenced by the degree of β-cell loss, quantity of functional β-cell mass, anthropometric factors (e.g., age, sex), and the aggressiveness of the self-directed immune response. Also key to this model is an embedded "stress test" hypothesis for T1D. Building on the three key quantitative facets of β-cell form and function, the quantity of β-cells present in early life represents a key agent of influence for the development of T1D. Specifically, in situations of limited (i.e., reduced) β-cell mass, this physiological setting creates de novo, a degree of stress that promotes a more rapid progression to overt T1D, independent of or beyond the need for additional environmental triggers. The figure was developed, in part, with intellectual contributions from Richard Insel, JDRF, and Alvin Powers, Vanderbilt University.

on adherence to the natural history model of T1D (Fig. 5), a concept has arisen that within a modest time of disease onset, individuals have an absolute loss of C-peptide production alongside of an absence of pancreatic β-cells.

The reality is that a growing body of evidence suggests quite the opposite, that many patients with T1D retain β-cells long after their diagnosis and, in agreement with this finding, that a majority of subjects retain the ability to produce C-peptide long after disease onset (46). To the former issue, studies of both intermediate- to long-term duration, as well as long-standing subjects with T1D (i.e., Joslin Medalists), all demonstrate residual β-cells in a majority of patients (31,47,48). The pathology described was unusual in that β-cells were largely observed as being focal and lobular in their distribution or often observed as scattered single or small clusters of cells in specific lobes. In the study by Gianani et al. (31), the authors also posed two unique patterns of islet composition and β-cell localization: pattern A, a mix of insulin-deficient and insulin-containing islets, and pattern B, where all islets contain β-cells. Interestingly, this form of lobular distribution is similar to the lobular descriptions ascribed to insulitis, noted earlier (49).

Moving forward, these studies support additional research efforts designed to understand the factors (e.g., age at onset, genetics, treatment) that influence β-cell persistence, as such information could prove vital for the development of therapeutic interventions designed to preserve β-cell function.

Streetlight #7—T1D Is a Single Disease
In recent years, much progress has been observed in the efficacy of treatment for several autoimmune diseases, with one of the bases for said progress being not only the development of improved therapeutics but also the clear identification of disease subclasses. Misleadingly obvious, the recognition that an autoimmune disease is rarely a single disease (i.e., heterogeneous) with identical manifestations and behavior in all individuals is in reality a fundamental flaw, leading to unexpected and undesired consequences. With insulin being the only approved therapy for T1D, little attempt has been made to evaluate disease heterogeneity from a pathogenic perspective. However, the disease that appears in a 3-year-old child who has T1D-associated autoantibodies, exceedingly low C-peptide levels, and disease-predisposing HLA genes and who may also possess celiac disease cannot easily be likened to the disease whose onset occurs in a 40-year-old patient with limited HLA risk, detectable C-peptide, and no other autoimmune diseases.

A recent meta-analysis of 213 cases demonstrated that insulitis occurs in 73% of young (≤14 years) patients with T1D with short disease duration (i.e., 1 month) of onset, in contrast to only 29% of cases fitting the same criteria, but having a diagnosis between 15 and 40 years of age. In addition, at the time of diagnosis, patients with T1D over 15 years of age have twice the number of islets containing β-cells versus those ages 14 years and under (27). As to why such variances are present, one possibility relates to the aggressiveness of the processes of β-cell destruction as a function of age. Interestingly, adult cases are characterized by a reduced frequency of HLA susceptibility haplotypes, as compared with children, and overall have less acute symptoms than children. Male predominance is a further, unexplained feature of T1D in young adults (reviewed in 50). Beyond this, T1D as expressed in adults may be less fulminate, with fewer islets affected. This property may, in part, represent one of the major reasons the diagnosis of T1D may be underdiagnosed in adults.

Overall, it is important that future efforts, like the one recently and nicely taken by Peakman and colleagues (51), be directed at better understanding disease heterogeneity for the impact it would have on diagnosis, treatment, and even intervention. Indeed, to the latter notion, such heterogeneity may aid in both the enrollment of disease intervention trials as well as improved therapeutic outcomes.

Streetlight #8—T1D and T2D Represent Two Different Diseases
T1D is near-universally recognized as a condition of absolute insulin deficiency that derives from the selective destruction of β-cells, whereas T2D is largely attributed to insulin resistance (26). Thus, they are widely considered two diverse diseases in terms of their pathogenesis. However, increasing clinical evidence shows that these two diabetic conditions overlap markedly.

A partial listing of such indications would include *1)* immunological phenomena (e.g., T1D-associated autoantibodies, elevated circulating cytokines and chemokines) classically associated with T1D also appear in many patients with T2D (52); *2)* obesity, which is associated with insulin resistance and T2D, shows strong correlations with the recent increased incidence of T1D (53); *3)* insulin resistance is a risk factor for the progression of T1D (54); *4)* amyloid is present in the pancreas of those with T1D; and *5)* β-cell destruction appears not only in T1D but also in T2D (55). Not surprisingly, therefore, the classification of diabetes into two main types, and even the autoimmune nature of T1D, has recently been challenged (56). Beyond this, through differential gene expression analysis, Chaparro et al. (57) provided strong genetic evidence for the overlap in pathologies and thus have impacted this debate substantially. Interesting, reports have also shown familiar clustering of T1D and T2D genes, with recent studies suggesting that selected susceptibility gene variants may be involved in the pathogenesis of both forms of diabetes (58).

MOVING FORWARD—THE BENEFITS OF MOVING OUTSIDE OF THE STREETLIGHT
While noting eight streetlights, which are clearly of particular interest to us, other examples exist and likely

would also benefit from reflection and unbiased questioning. Why (in the eyes of many observers) is the field of T1D research apparently stalled? Why did so many expensive programs fail to meet their objectives? Why does so much of T1D research focus on initiation and precipitation of disease instead of the fact that the intervening period may last for decades? Beyond the streetlights noted, others may disagree with our usage of the concept in each setting, perhaps viewing such facets as being subject to "status quo bias" or "the bandwagon effect." Here, we would note the potential for these streetlights to be subjected to multiple forms of bias. More than arguing terminology, our hope in composing this Perspective is to draw further attention to the importance of these concepts to T1D research.

"Paradigms" are universally recognized (but necessarily finite) constructs that temporarily model problems and solutions for a community of researchers. As such, paradigms have the potential to be very useful, constituting invaluable instruments with which to judge experiments and results. However, if unchallenged and eventually taken to represent dogma, they constrain freedom of thought and severely impede the advancement of knowledge, which brings us to a famous quote by Mark Twain: "Whenever you find yourself on the side of the majority, it is time to pause and reflect" (59).

In an effort to accept Twain's advice and as conveyed in this Perspective, we indicate a number of facets at the forefront of T1D research, given their majority thought in the presence of limited (or diminishing) evidence, that require intellectual and experimental revaluation. We admit this Perspective has the potential to suffer from our own personal biases, and our contentions may, over time, be proven errant. Time will tell. Indeed, the field is poised, in a variety of ways (e.g., technology, communications, sample availability, methods for data analysis), to come out from underneath the streetlight and test new hypotheses. It is our belief that such action will have great potential to gain insights capable of impacting those with T1D.

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