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The Streetlight Effect—Is There Light at the End of the Tunnel?

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Autoimmune type 1 diabetes research and treatment are seemingly plagued with problems. Large and small, mostly well-thought out clinical studies and trials since the early 1980s have basically been negative. None of the treatments tested have reached clinical routine to replace current lifesaving insulin replacement therapy. A combination type of therapy to diminish the requirement for insulin is yet to be found. The chronic autoimmune disease at the time of clinical onset of type 1 diabetes has been the "winner" in all attempts made so far to stifle the disease process. The disease is also the "winner" over islet transplantation, a potential cure for diabetes. Islet transplantation research was drastically reduced after it was found that the so-called Edmonton protocol did not yield sustainable insulin independence despite short-term restoration of endogenous insulin production and glycemic stability (1). The Diabetes Control and Complications Trial (DCCT) study, well known to all, continues to underscore the importance of glucose control. The reduction in the risk of complications resulting from intensive therapy in patients with type 1 diabetes persisted at least for 4 years after the study was completed, despite increasing hyperglycemia (2). Notwithstanding progress in the overall diabetes management, we were all recently reminded of the fact that type 1 diabetes remains a deadly disease (3). Although mortality was the highest in patients with poorly controlled diabetes, it was reported that patients with type 1 diabetes with A1C of 6.9% or lower had a risk of death from any cause that was twice as high as the risk for matched control subjects (3). Against this background of an uphill battle, the current issue of *Diabetes* contains a Perspective by Battaglia and Atkinson entitled "The Streetlight Effect in Type 1 Diabetes" (4).

In their Perspective, the authors put forward several remedies to the question of why progress is slow in type 1 diabetes research to uncover its etiology and pathogenesis. They argue that the type 1 diabetes landscape has become difficult to traverse because of the increasing pressure from both funding agencies and patients, uncertainties of data replication, and the growing lack of faith in so-called animal models. The authors indicate that type 1 diabetes research has degenerated to a science of replication that avoids the real questions. Little efforts are made to dispute existing dogmas and disprove current hypotheses. Exploration in the dark is both difficult and unpleasant as it may lead to nothing. The authors illustrate their frustrations by using the well-known comic strip that illustrates the story about the man searching for a quarter under a lamppost because the light is better there as compared with the darkness over where he dropped it.

Although the original comic strip has many iterations (Fig. 1), many readers are likely to have a smile of recognition. They have seen this before. Battaglia and Atkinson use the comic strip as a phenomenon of observational bias (4). However, it is useful in more than one way. In lectures and teaching on insulin therapy, it has been useful to illustrate that insulin injected subcutaneously (under the light) is poor to reach its major target, the liver (in the dark). Insulin treatment remains a practice where the replacement is given at the wrong site, in the wrong amounts, and at the wrong time.

Another example of how to use the comic strip is to illustrate the view that it is easier to replicate what others have done as opposed to make observations that nobody has made before. It is safer to be in the streetlight rather than being out there in the darkness searching for the unknown. "The great tragedy of Science," wrote Thomas Henry Huxley, is "the slaying of a beautiful hypothesis by an ugly fact" (5). More ugly facts emanating from the dark are needed if type 1 diabetes research in etiology and pathogenesis will progress. It is also easier to get your paper published, as reviewers tend to be friendlier to observations that corroborate.

A third way to look at the comic strip is that researchers have been looking where the light is because they do not know better. In type 1 diabetes etiology and pathogenesis research, the effort has been focused at the

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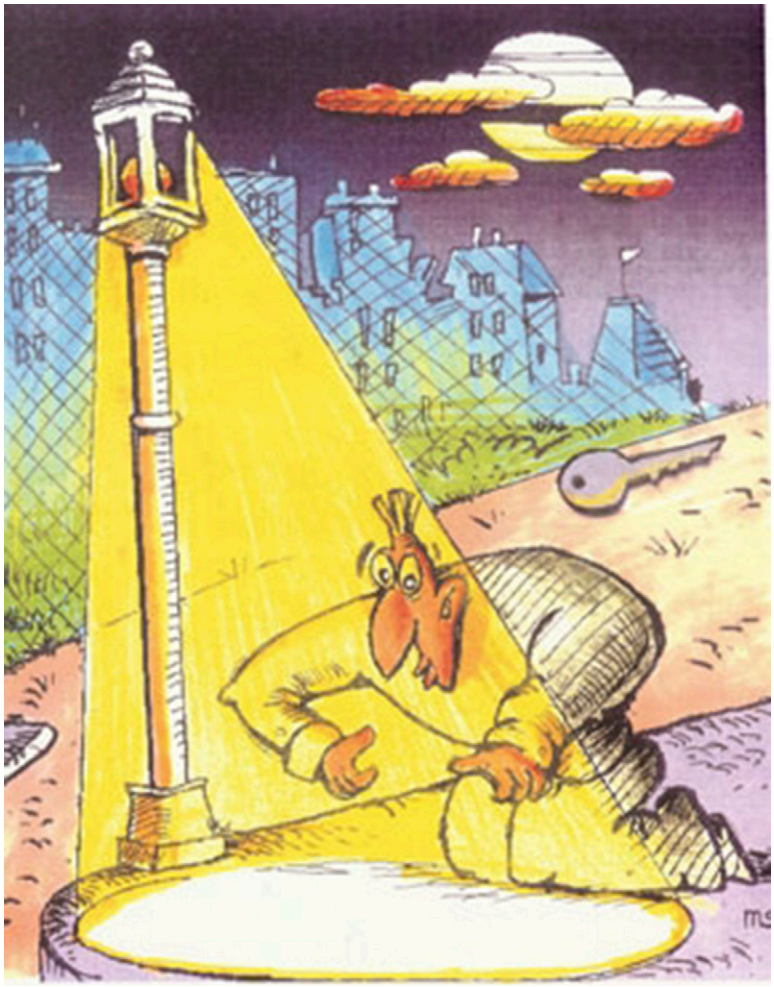

Figure 1— The streetlight effect. The key is in the dark but the search is where the light is (https://en.wikipedia.org/wiki/Streetlight_effect).

time of clinical diagnosis. That is where the light is. The long-term view has been that type 1 diabetes was an acute-onset disorder characterized by the typical symptoms of weight loss, polydipsia, polyphagia, and polyuria. The disease onset is rampant and develops quickly, hence the etiology ought to be around the corner—weeks, perhaps a month or so at best. No surprise that an etiology involving a virus developed quickly based primarily on case reports (6) and that insulitis at the time of clinical onset was the most likely cause of β-cell demise (7). The association with HLA (8) and the demonstration of islet cell antibodies in diabetes, associated not only with autoimmune polyendocrine diseases (9) but also at the time of clinical diagnosis in the very young (10), closed the gap to type 1 diabetes being dubbed as an autoimmune disease to conform with the hypothesis that was put forward much earlier by Mackay and Burnet as pointed out by Battaglia and Atkinson (4).

It is interesting to note that when islet cell antibodies were first found among first-degree relatives of patients with type 1 diabetes the specificity of the method was questioned. It was not until prospective studies were carried out in families that it was realized that the disease process might have started much earlier than had been appreciated (11). The streetlight effect of looking where the light was—i.e., at the time of clinical diagnosis—therefore took its toll on slowing down progress toward the understanding of the etiology of diabetes. And still does! However, investigators have now moved away from the "onset streetlight" into the darkness by dissecting the disease process from birth and onwards until one islet autoantibody appears as a marker of a disease process that eventually will lead to the clinical onset of diabetes. The chances to make a breakthrough to uncover the etiology of type 1 diabetes have increased. However, it cannot be excluded that investigators have lit a new streetlight by a focus on the appearance of a first islet autoantibody (12–14). A true breakthrough would come with a biomarker—perhaps a test for antigen-presenting cells, a T cell, or something completely different—that clearly marks the initiation of a pathogenesis that months or years later results in a clinical onset. At present, two or more of autoantibodies against either insulin, GAD65, IA-2, or zinc transporter 8 (ZnT8) mark a pathogenesis

that within 20 years of follow up results in 100% diabetes in the affected (13).

Battaglia and Atkinson (4) list eight streetlights that hamper progress. They are all useful points. However, is it not time to stop pussyfooting around and start the identification of the etiology of type 1 diabetes? Now we know that the clock to clinical onset has started once one or two islet autoantibodies have appeared (13). Should not all efforts be focused to retire the islet autoantibodies to find a marker of the etiology that explains the subsequent pathogenesis? The ideal marker perhaps would be the trigger and the etiological agent. In the best of worlds, the trigger may be the same as an etiological factor but it does not have to. The problem with explaining the etiology of type 1 diabetes is that most studies, including the laudable efforts to better understand the genetic etiology of type 1 diabetes (15), have been carried out under the streetlight of clinical onset, not when islet autoantibodies were first detected. Recent data suggest that there may be other genetic factors that are associated with the onset of islet autoantibodies (16). Many of the type 1 diabetes genes therefore may be associated with the pathogenesis. As the majority of the type 1 diabetes genes appear to be related to T lymphocytes (15), the efforts to dissect the genetics of type 1 diabetes would support the hypothesis that type 1 diabetes pathogenesis is autoimmune. But it has been done under a streetlight shining at the very end of a long process of losing β-cells in numbers and function.

Taken together, type 1 diabetes is a very serious disease that is increasing worldwide and is a deadly disease. Observational bias is a risk factor that hampers progress to understand the etiology. It seems to be less of a risk factor to understand and perhaps manage the pathogenesis. However, it is often said that a cure is not to be expected unless we understand the etiology. Longitudinal studies from the birth of children at risk will hopefully provide ugly facts that will slay a few hypotheses—beautiful as they may be.

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References

1. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355:1318–1330

2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389

3. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972–1982

4. Battaglia M, Atkinson MA. The streetlight effect in type 1 diabetes. Diabetes 2015;64:1081–1090

5. Huxley TH. Biogenesis and abiogenesis. In *Collected Essays: Discourses, Biological and Geological.* Cambridge University Press, Cambridge, U.K., 1870, p. 229–271

6. Yoon JW, Austin M, Onodera T, Notkins AL. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N Engl J Med 1979;300:1173–1179

7. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes 1965;14:619–633

8. Nerup J, Platz P, Andersen OO, et al. HL-A antigens and diabetes mellitus. Lancet 1974;2:864–866

9. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 1974;2:1279–1283

10. Lendrum R, Walker G, Gamble DR. Islet-cell antibodies in juvenile diabetes mellitus of recent onset. Lancet 1975;1:880–882

11. Gorsuch AN, Spencer KM, Lister J, et al. Evidence for a long prediabetic period in type I (insulin-dependent) diabetes mellitus. Lancet 1981;2:1363–1365

12. Ilonen J, Hammais A, Laine AP, et al. Patterns of β-cell autoantibody appearance and genetic associations during the first years of life. Diabetes 2013;62:3636–3640

13. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479

14. Akolkar B; Teddy Study Group. The six-year incidence of diabetes associated autoantibodies in the genetically at-risk: the TEDDY Study. Presented at the Immunology of Diabetes Society 13th Congress, 7–11 December 2013, at the Mantra Resort, Lorne, Australia

15. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med 2009;360:1646–1654

16. Törn C, Hadley D, Lee H-S, et al.; the TEDDY Study Group. Role of type 1 diabetes associated SNPs on risk of autoantibody positivity in the TEDDY Study. Diabetes. 24 November 2014 [Epub ahead of print]. DOI:10.2337/db14-1497