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Lernmark, Åke

Published in:
Diabetes

DOI:
10.2337/db15-0011

2015

DB14-1208.R1

Commentary to "The streetlight effect in type 1 diabetes" by Manuela Battaglia1 and Mark A. Atkinson.

The streetlight effect – is there light at the end of the tunnel?

Åke Lernmark

Department of Clinical Sciences, Lund University/CRC, Skåne University Hospital, Malmö, Sweden

Corresponding author:

Åke Lernmark, professor

Lund University/CRC

Department of Clinical Sciences

Jan Waldenströms gata 35

Skåne University Hospital SUS

20502 Malmö, Sweden

Phone: +46 40 39 19 01

Autoimmune type 1 diabetes research and treatment is seemingly plagued with problems. Large and small, mostly well thought out clinical studies and trials since the early 1980ies have basically been negative. None of the treatments tested have reach clinical routine to replace current life-saving 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 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 type 1 diabetes patients persisted at least for four 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 poorly controlled

diabetes patients, it was reported that type 1 diabetes patients with HbA1c of 6.9% or lower had a risk of death from any cause that was twice as high as the risk for matched controls (3). Against this background of an uphill battle, the present issue of Diabetes is running a *Perspectives* by Atkinson and Battaglia entitled "The Streetlight Effect in Type 1 Diabetes (4).

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

Although the original cartoon has many followers, many readers are likely to have a smile of recognition. They've seen this before. The authors of the *Perspectives* employ the cartoon as a phenomenon of observational bias (4). However, the cartoon is useful in more than one way. In lectures and teaching on insulin therapy, the cartoon 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 how to use the cartoon 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 is 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 Streetlight cartoon 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 time of clinical diagnosis. That's were 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 was rampant and developed 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 beta-cell demise (7). The association with HLA (8) and the demonstration of islet cell antibodies (ICA) in diabetes not only associated 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 Atkinson and Battaglia (4).

It is interesting to note that when ICA was first found among first degree relatives to type 1 diabetes patients 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 towards 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 mark 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 ZnT8 mark a pathogenesis that within 20 years of follow up results in 100% diabetes in the affected (13).

Atkinson and Battaglia (4) is listing eigth 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). Shouldn't all efforts be focused to retire the islet autoantibodies to find a marker of the etiology that explain the subsequent pathogenesis? The ideal marker would perhaps the trigger and the etiological agent all the same. In the best of worlds the trigger may be the same as an etiological factor but it does not have to. The problem to explain 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). The effort has been carried out under the streetlight of clinical onset, not when islet autoantibodies were fist 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 may therefore be associated with the pathogenesis. Since 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 beta cells in numbers and function.

Taken together, type 1 diabetes is a very serious disease that is not only increasing worldwide but is also 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 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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