LETTER

Viral underpinning to the Austrian record of type 2 diabetes?

Thurner et al. (1) identifies spikes in diabetes incidence using year-of-birth data from Austria over the last century. They intriguingly associate these peaks with intervals of nationwide famine with the disease onset apparently occurring decades later. The information provided by Thurner et al. is a valuable supplement to previous studies on the Dutch WWII famine that also demonstrate a relationship to later diabetes onset (2). Based on our studies of a rodent-borne Picornavirus*, we suggest an alternative interpretation involving an infectious contribution to the diabetes.

The Ljunganvirus, first identified in native rodents of Europe and North America, was later found correlated with the diabetes incidence in Northern Sweden and associated with population outbreaks of the rodents, along with the observations that the rodents themselves experienced diabetes. A laboratory mouse model in which pregnant dams were exposed to the virus is especially pertinent to the interpretation of diabetes in those exposed to the Austrian famines: at maturity offspring exposed in utero became diabetic, but only if exposed to stressful conditions. The external stressors, either behavioral or metabolic, were essential for the disease outcome even in the presence of the virus. Another experiment* showed that the diabetic symptoms were reduced or eliminated following antiviral treatment, pointing to a causative role for the virus itself.

Viral involvement in diabetes susceptibility may play out as follows. A conditioning stimulus of diabetes susceptibility occurs with viral infection of the mother during pregnancy. Viral success is enhanced by stressors through immune modulation in response to stress in a pregnant host. The virus influences tissue development in the embryo, conditioning susceptibility to diseases occurring later in life. Disease expression itself depends on the conjunction of several factors, such as lifestyle, adiposity, and genetics.

In type 1 diabetes (T1D), a trigger, typically associated with a viral source (3), has been postulated as occurring 2 y before diabetes onset. Although the Austrian diabetes cases were largely type 2 diabetes (T2D), with most case subjects aged over 50 y, physiological connections between T1D and T2D are now well established, suggesting links between the two (4, 5). Characteristics of both T1D and T2D have been noted in the rodents in which the Ljunganvirus was first identified. The timing of the periods of famine relative to the birth dates of individuals later acquiring diabetes in the Austrian sample is critical. For each of the Austrian famines (1), it is noted that the births occur within 2 y of the famine episode. Thurner et al. (1) interpret this timing as being a result of the famine itself, yet this pattern corresponds with the behavior of a viral trigger. For the Austrian diabetes record the stress may have been an essential event encouraging viral infection to alter development, permitting T2D decades later. Although a viral hypothesis in diabetes causation has long been discussed, the Ljunganvirus hypothesis fits this new data. Both viral trigger and social stress hypotheses have been around for many years, and both may prove essential to an understanding of diabetes etiology.

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1 Thurner S, et al. (2013) Quantification of excess risk for diabetes for those born in times of hunger, in an entire population of a nation, across a century. *Proc Natl Acad Sci USA* 110(12):4703–4707.

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3 Knip M, Simell O (2012) Environmental triggers of type 1 diabetes. *Cold Spring Harb Perspect Med* 2(7):a007690.

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5 Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C (2011) Vitamin D and diabetes: Its importance for beta cell and immune function. *Mol Cell Endocrinol* 347(1–2):106–120.

Author contributions: W.K. and B.N. wrote the paper.

Conflict of interest statement: B.N. is associated with Apodemus AB, which includes Ljunganvirus research.

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*See www.ljunganvirus.org for references.

www.pnas.org/cgi/doi/10.1073/pnas.1305074110