NIH Research To Prevent Type 1 Diabetes: George Eisenbarth's Legacy

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WE REMEMBER GEORGE EISENBARTH for his many contributions to the scientific understanding of the pathogenesis of type 1 diabetes (T1D). In this article we frame our discussion of Dr. Eisenbarth's legacy, citing quotations from a noted scientific philosopher of the modern era, David Hume:

The sweetest and most inoffensive path of life leads through the avenues of science and learning; and whoever can either remove any obstructions in this way, or open up any new prospect, ought so far to be esteemed a benefactor to mankind.

—David Hume, 1748

George Eisenbarth certainly followed the “sweet and inoffensive path of life through science,” and those with the good fortune to join him along the way were enriched and sincerely grateful for his guidance and good company. Eisenbarth was also known for “removing obstructions and opening up new prospects.” In part, the impact of his contributions can be measured by the citation of his work by others, the scientific product of the many people he trained, and his service to the community through National Institutes of Health (NIH) peer review.

According to the bibliographic search service SCOPUS, George Eisenbarth was listed as an author on 548 published articles from 1998 to 2012. His articles were cited by 15,493 other articles (excluding self-reference) during this period of time. Excluding reviews, chapters and books, Eisenbarth co-authored 406 original published reports from 1973 through 2012. One of his most frequently cited articles is “Type 1 diabetes: a chronic autoimmune disease,” published in the *New England Journal of Medicine* in 1986.¹ This article characterizes the pathogenesis of T1D as a progression from genetic susceptibility through environmental triggers and gradual β -cell destruction. This model has withstood the test of time and continues to guide the field toward its goal of preventing the disease.

Other frequently cited and notable articles from Eisenbarth include “The insulin gene is transcribed in the human thymus and transcription levels correlated with allelic variation at the INS VNTR-IDD2 susceptibility locus for type 1 diabetes,”² “Prediction of type I diabetes in first-degree relatives using a

combination of insulin, GAD, and ICA512bdc/IA-2 auto-antibodies,”³ and “Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice.”⁴ These articles are part of the rationale for insulin administration for desensitization to prevent T1D. This idea was first investigated in the Diabetes Prevention Trial Type 1 (DPT-1). This study showed possible efficacy in the oral insulin subgroup with the highest insulin antibody titers,⁵ which TrialNet is attempting to verify in its current oral insulin trial. In addition, Eisenbarth's early article from his days as an NIH fellow, authored with Nobelist Marshall Nirenberg, “Monoclonal antibody to a plasma membrane antigen of neurons,”⁶ remains one of the most highly cited articles from Nirenberg's neurobiology period. This article is still cited by neurobiologists every year, demonstrating the durability of even one of Eisenbarth's earliest contributions.

Eisenbarth was continuously funded by the NIH since 1979, including a prestigious MERIT award in 1992 from the National Institute of Diabetes, Digestive, & Kidney Diseases (NIDDK). This funding history represents a major achievement for any investigator and is a reflection of his research productivity, his ability to identify important problems for investigation, his knack for effective communication, and his capacity to embrace constructive disagreement. Eisenbarth welcomed scientific discussion gladly and eagerly, even when it challenged his own most strongly favored hypotheses.

Indulge your passion for science, says she, but let your science be human, and such as may have a direct reference to action and society.

—David Hume, 1748

Eisenbarth's scientific interests followed Hume's prescription in being focused on that which has the potential to alleviate human suffering. He chose important problems that necessitated solution and did not shy away from technically difficult challenges. Eisenbarth played a key role in efforts to standardize antibody measurements internationally so that results can be compared across studies and measurements can reliably be performed in multiple labs. The scientific rigor and attention to practical considerations Eisenbarth brought to

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screening technology will be needed to identify people at risk. NIDDK is funding research to develop simpler and cheaper tests through a Small Business Innovation Research award to a company that Eisenbarth attracted to the field of T1D research. This work continues to emerge, striving to simplify and remove the significant obstacle of expensive and technically difficult autoantibody measurement through technological innovation. Eisenbarth recognized that without cost-effective and reliable risk screening technology in hand, the field will not be ready to identify people at risk and to intervene to prevent the disease, even if effective strategies are identified.

Eisenbarth was a consultant to the Congressionally established Diabetes Research Working Group that produced *Conquering Diabetes: A Strategic Plan for the 21st Century*.^{7,8} A decade later he was a member of the Type 1 Diabetes and Autoimmunity Working Group that contributed to development of the current Diabetes Strategic Plan issued in 2011. These activities are critically important for informing the public as well as Congress about the importance of diabetes research and the burden of T1D on the population.

Eisenbarth was a dedicated peer reviewer. He participated in 41 NIH review meetings spanning two decades. He was also an engaged and active consortium member, serving on many committees within TrialNet, TEDDY, and other large clinical research networks. Eisenbarth provided leadership in laboratory monitoring activities and the practical aspects of clinical trial operations in addition to his conceptual scientific leadership mentioned previously.

Eisenbarth's work has had global impact, which is in no small part due to his active training of the next generation of scientists. Eisenbarth's 40 trainees are located at institutions around the world (Fig. 1). IN-SPIRE,⁵ a text analysis tool, was used to evaluate up to 100 published abstracts from each of 37 of George Eisenbarth's trainees (a total of over 1,000 abstracts), and the results are graphically represented in Figure 2. This analysis shows the depth and breadth of diabetes research as a result of Eisenbarth's exemplary mentorship.

George Eisenbarth's outstanding scientific achievements, and his service to the community of T1D researchers, have brought us a good way closer to preventing the disease. We can expect to continue to enjoy being reminded of George Eisenbarth as we progress along the pathway toward new therapies to treat and prevent T1D. His living legacy consists of the many scientists he mentored and the colleagues he inspired as the epitome of a creative, compassionate, and caring physician and scientist.

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