

Insulin Glargine Controversy: A Tribute to the Editorial Team at *Diabetologia*

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Progress in biomedical research is documented in journals after peer review, a process with flaws but the best we have. Once an article is published, in general it faces three fates. Most commonly, after some measure of initial interest, it quietly slips into obscurity, only occasionally to resurface if cited by a vigilant successor who recognizes the prior contribution to a once again advancing field. A quick glance through a copy of any major medical journal published ≥ 50 years ago is a humbling experience for any active scientist. Many of the confidently stated conclusions, with hindsight, were quite simply wrong. How many of our conclusions today will seem mildly amusing to a reader 50 years from now? Occasionally, an article makes a tremendously important contribution that advances a field and is widely cited, becoming a so-called citation classic with little controversy. Reading such a paper that is ≥ 50 years old can also be a humbling experience. How did the authors have such insight from what we now consider an incomplete dataset obtained by insensitive and nonspecific methods compared with those available to us now?

It was clear to the editorial team at *Diabetologia* that an article recently submitted to that journal was one that fell into a third category (1)—an article that is likely to incite immediate controversy. Typically, such an article, once published after peer review, then stands or falls as a result of wider scrutiny by scientific peers. At first sight, it would seem that the early controversy is harmless enough if the authors are willing to stand the heat in the kitchen. However, there is an important exception to this in biomedical research: if the conclusion of the paper might alter clinical practice in such a way that patients can be harmed or contains information that might lead to unnecessary concern for patients if the information reaches the general media.

When an article that reported an increased incidence of cancer in people using insulin glargine (1) was submitted to *Diabetologia*, the editors took extraordinary steps. Not only was the article subject to the usual peer review, but before publishing the study, the editors solicited additional studies from investigators with epidemiological databases from several nations (2,3,4). Is such expediency by editors of a journal typical? I think we have to agree that the answer is no. The resulting studies were then published together in a recent edition of *Diabetologia*

along with a cautiously worded editorial and a statement from the journal's host organization (5), the European Association for the Study of Diabetes. The accompanying editorial was careful to point out that the assembled data, while raising some concern whether insulin glargine might increase the risk of cancer, were not definitive and indicated the need for additional studies. The purpose of this editorial is not to join the ongoing debate about the increment in risk, if any, of the use of insulin glargine to treat diabetes. As the editors of *Diabetologia* conclude, the debate can only be resolved by further studies, which may or may not be performed.

Rather, the purpose of this editorial is to serve counterpoint to some quite harshly worded statements published rapidly after the *Diabetologia* articles and the accompanying editorial. "Insulin Glargine and Malignancy: An Unwarranted Alarm" is the title of a comment published in *The Lancet* (6). "Insulin Glargine and Cancer—An Unsubstantiated Allegation" is the title of an editorial in *Diabetes Technology & Therapeutics*, under the heading of which the authors confer themselves high honor by citing Charles Darwin, "to kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact" (7). Based on the flurry of correspondence and phone calls coming to those of us who prescribe insulin, the most apparent "alarm" following the publication of the articles in *Diabetologia* was that of the company that sells insulin glargine. And with due respect to Charles Darwin, we are not sure he would yet agree that an error has been perpetrated given the cautious conclusions of the *Diabetologia* editorial. Practicing physicians were for the most part content with the measured statements that were released by the national organizations, and patients do not seem unduly alarmed.

In contrast to some of the rather strident editorial comments published in response to the articles and the editorial in *Diabetologia*, we at *Diabetes* offer our congratulations to the editorial team at *Diabetologia* for taking such extraordinary measures to obtain the additional studies and to write a carefully balanced editorial to go with the first submission that they received. The assembled articles have drawn attention to the long-known but little-investigated link between type 2 diabetes and cancer (5). It is now much better appreciated that metformin therapy decreases cancer risk (4,8,9). Based on the assembled data, use of higher dose of insulin therapy may accelerate the growth of existing cancers (5). As the editorial in *Diabetologia* points out, the question whether long-acting insulin analogs have an additional effect on cancer risk remains unresolved but, based on the available evidence, deserves further study.

Taking the 50-year perspective alluded to above, we are confident that the editorial accompanying these articles in *Diabetologia* will age well. Moreover, it is surely the responsibility of the scientific community and journal

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editors to raise concerns about the possibility of unintended adverse consequences of an available therapy, as unpalatable as such concerns may be for those who market the product.

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